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(54) Title: METHODS AND COMPOSITIONS FOR TREATING AIDS AND HIV-RELATED DISORDERS USING 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, OR 46777

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of AIDS or an HIV-related disorder or disorders. Specifically, the present invention identifies the differential expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, and 46777 genes in tissues relating to AIDS or an HIV-related disorder, relative to their expression in normal, or non-AIDS or HIV-related disease states, and/or in response to manipulations relevant to AIDS or an HIV-related disorder. The present invention describes methods for the diagnostic evaluation and prognosis of various HIV-related disorders, and for the identification of subjects exhibiting a predisposition to such conditions. The invention also provides methods for identifying a compound capable of modulating AIDS or an HIV-related disorder or disorders. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of AIDS or an HIV-related disorder.

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METHODS AND COMPOSITIONS FOR TREATING AIDS AND HIV-RELATED DISORDERS USING 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 OR 46777

Related Applications

[0001] The present application claims the benefit of U.S. Provisional Application Serial No. 60/454,202, filed on March 12, 2003, of U.S. Provisional Application Serial No. 60/456,326, filed on March 20, 2003, of U.S. Provisional Application Serial No. 60/465,240, filed on April 24, 2003, of U.S. Provisional Application Serial No. 60/475,233, filed on June 2, 2003, of U.S. Provisional Application Serial No. 60/478,952, filed on June 16, 2003, of U.S. Provisional Application Serial No. 60/487,836, filed on July 16, 2003, and of U.S. Provisional Application Serial No. 60/500,111, filed on September 4, 2003. The entire contents of these provisional patent applications are hereby incorporated in their entirety by this reference.

Background of the Invention

[0002] Human Immunodeficiency Virus (HIV) is a member the lentivirus genus of the *Retroviridae* family. On the basis of serologic properties and sequence analysis of molecularly cloned genomes human lentivirus isolates are designated HIV-1 and HIV-2. A classification scheme based on the sequence of the viral envelope (env) protein recognizes several subtypes/clades (e.g. HIV-1 A-I). Viral diversification is a key feature of HIV phylogeny. Each subtype displays a high degree of variability. Mutations introduced by the error-prone viral reverse transcriptase represent the major factor for variation, but also recombination occurs within individuals infected with different clades. Molecular epidemiology studies indicate, that viral migration/trafficking rather than viral mutation is the ecologic driving force for the pattern of global variation and distribution.

[0003] HIV represents an enveloped virus with two identical copies of a (+)-stranded RNA genome of 9.2 kb in length coding for 9 structural and regulatory viral proteins. Initial steps of infection are mediated through specific interaction of the viral envelope glycoprotein and the major host cell receptor CD4 as well as specific coreceptors CXCR4 (T-troph)/CCR5 (M-troph). After penetration virion RNA is converted into double-stranded DNA by the viral reverse transcriptase. Concomitantly, viral integrase and host cell proteins carry out integration

of the linear DNA into the host cell genome to produce the provirus. This intracellular genomic form represents the template for synthesis of full length genomic or subgenomic (spliced and unspliced forms) single-stranded viral RNAs catalyzed by the cellular RNA polymerase II.

[0004] HIV encodes precursor polyproteins as well as additional open reading frames. The ***gag***, ***pol*** and ***env*** genes encode precursors for the virion capsid proteins, several virion enzymes (protease, reverse transcriptase/RNAse H, integrase) as well as the envelope glycoprotein, respectively. The transcriptional activator (***tat***) and regulator of viral transcription (***rev***) encode nonstructural essential proteins. In contrast ***vif***, ***vpr*** (HIV-1), ***vpu*** (HIV-2) and ***nef*** encoded genes represent nonessential 'accessory' proteins, which are thought to exert their pleiotrophic regulatory/modulatory effects through specific interactions with several different host cell encoded proteins.

[0005] Based on an intimate host/virus relationship at each step the viral life cycle is susceptible to inhibiting host cell functions. A summary of examples (see section 4.2) will illustrate the mutual relation. With the exception of the lentiviruses productive infection of target cells by most retroviruses is dependent upon proliferation and concomitant nuclear membrane dissolution of the infected cell. Lentiviruses such as HIV can infect nonproliferating cell types such as macrophages and other terminally differentiated cells overcoming the need for cell division. Activated and resting CD4-positive T helper cells as well as macrophages represent the major target cells for HIV. The role of dendritic cells as well as glia cells in HIV propagation and (neuro)-pathogenesis is discussed controversially.

[0006] HIV has been shown to be the etiologic agent of the acquired immunodeficiency syndrome (AIDS). The virus is transmitted by exposure to body fluids of an infected person. Sexual transmission, blood transfusions as well as intravenous drug abuse comprise the major routes. Infection with HIV is characterized by relentless and progressive decline in both number and function of CD4-positive T helper lymphocytes, which play a central role in coordinating immune responses. Ultimately, the weakened immune system is unable to control and eradicate the virus, AIDS develops, which is often accompanied with other opportunistic infections. In the four decades that HIV has afflicted the human population virus spread led to the death of over 22 Million people. It is estimated that about 36 million people worldwide are infected with HIV.

[0007] Antiretroviral drug therapy mainly encompassing different combinations of nucleosidic, non-nucleosidic inhibitors of the viral reverse transcriptase as well as protease

inhibitors has dramatically improved the lives of those who receive drug treatment. However, current therapies only delay progression of illness and are unable to eradicate the virus. Moreover, drug resistance reappears as a significant problem, close to 50% of the patients fail to efficiently suppress viral replication on treatment mainly due to resistance issues and tolerability/compliance of current drug regimens. Thus, additional HIV therapies are urgently required.

Detailed Description of the Invention

[0008] The present invention provides methods and compositions for the diagnosis and treatment of AIDS and HIV-related disorders.

[0009] "Treatment", as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease or disorder, a symptom of disease or disorder or a predisposition toward a disease or disorder, with the purpose of curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving or affecting the disease or disorder, at least one symptom of disease or disorder or the predisposition toward a disease or disorder. A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides. Representative molecules are described herein.

[0010] The present invention is based, at least in part, on the discovery that nucleic acid and protein molecules, (described infra), are differentially expressed in disease states relative to their expression in normal, or non- disease states. The modulators of the molecules of the present invention, identified according to the methods of the invention can be used to modulate (*e.g.*, inhibit, treat, or prevent) or diagnose a disease, including, but not limited to, AIDS and HIV-related disorders.

[0011] "Differential expression", as used herein, includes both quantitative as well as qualitative differences in the temporal and/or tissue expression pattern of a gene. Thus, a differentially expressed gene may have its expression activated or inactivated in normal versus disease conditions. The degree to which expression differs in normal versus disease or control versus experimental states need only be large enough to be visualized via standard characterization techniques, *e.g.*, quantitative PCR, Northern analysis, subtractive hybridization. The expression pattern of a differentially expressed gene may be used as part of a prognostic or diagnostic a disease, *e.g.*, AIDS and HIV-related disorders,

evaluation, or may be used in methods for identifying compounds useful for the treatment of a disease, *e.g.*, AIDS and HIV-related disorders. In addition, a differentially expressed gene involved in a disease may represent a target gene such that modulation of the level of target gene expression or of target gene product activity will act to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a disease condition, *e.g.*, AIDS and HIV-related disorders. Compounds that modulate target gene expression or activity of the target gene product can be used in the treatment of a disease. Although the genes described herein may be differentially expressed with respect to a disease, and/or their products may interact with gene products important to a disease, the genes may also be involved in mechanisms important to additional disease cell processes.

[0012] An "AIDS- or HIV-related cell", as used herein, includes, but is not limited to, thymocytes, dendritic cells, T cells, macrophages, peripheral blood mononuclear cells (PBMC) , lymphocytes, monocytes, leukocytes and lymphoid cells.

Molecules of the Present Invention

Gene ID 9145

[0013] The human 9145 sequence, known also as 11β-hydroxysteroid dehydrogenase (11β-HSD), is approximately 1348 nucleotides long including untranslated regions (SEQ ID NO:1). The coding sequence, located at about nucleic acid 102 to 980 of SEQ ID NO:1, encodes a 292 amino acid protein (SEQ ID NO:2).

[0014] As assessed by TaqMan analysis, 9145 mRNA expression was detected in thymocytes, dendritic cells, dendritic cell CD4+ T cell (DC/CD4) cocultures, T cells and macrophages. 9145 mRNA expression was highly induced by HIV infection in dendritic cells, DC/CD4, macrophages and thymocytes, and CD4+ T cells.

[0015] 9145 catalyzes the conversion of inactive cortisone to the active glucocorticoid cortisol. The principal glucocorticoid is cortisol. Cortisol is known to have a number of immunosuppressive effects including inhibition of mediators of inflammation, such as cytokines and prostaglandins. Cortisol inhibits production of IL-1 and IL-6 from macrophages and the production of inflammatory effects of bradykinin, platelet-activating factor and serotonin. Cortisol levels are elevated in HIV infected individuals which are correlated with disease progression. HIV patients have been demonstrated to have increased sensitivity to glucocorticoids due to enhanced receptor expression (*The Journal*

of Immunology, 2002, 169: 6361-6368). 9145 mRNA expression is primarily restricted to T cells, dendritic cells, macrophages and liver which contain large numbers of monocyte derived Kupfer cells. 9145 is induced to very high levels of expression following T cell and macrophage activation and following infection with HIV. The induction of 9145 may lead to increased cortisol levels locally and perhaps systemically which could lead to reduced immune responses including the production of proinflammatory cytokines, cytotoxic T cell and NK cell killing of virus-infected cells and enhanced viral replication. Therefore, inhibition of 9145 may decrease glucocorticoid levels, inhibit HIV replication and prevent the immunosuppressive effects of cortisol.

[0016] Due to 9145 mRNA expression in thymocytes, dendritic cells, dendritic cell CD4+ T cell (DC/CD4) cocultures, T cells and macrophages, along with its functional role, modulators of 9145 activity would be useful in treating AIDS and HIV-related disorders. 9145 polypeptides of the present invention are useful to screen for modulators of 9145 activity.

Gene ID 1725

[0017] The human 1725 sequence (SEQ ID NO:3), known also as angiotensin-converting enzyme, testis-specific isoform (ACE-T), is approximately 2478 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 29 to 2227 of SEQ ID NO:3, encodes a 732 amino acid protein (SEQ ID NO:4).

[0018] As assessed by TaqMan analysis, 1725 mRNA was highly expressed in macrophages, PBMC, tonsil and lymph node. 1725 mRNA was induced by HIV infection of CD4+ T cells, thymocytes, dendritic cells, dendritic cell/CD4+ T co-cultures and was highly expressed in the permissive Jurkat T cell clone 10H.

[0019] 1725 is a protease that is expressed at high levels in lymphocytes, dendritic cells and macrophages. 1725 is induced in macrophages by CD4+T cells (*Clin Exp Immunol*, 1992, 88(2):288-94) and is known to be involved in activation of CD4+ T cells. 1725 also has high levels of expression in lymphocytes, dendritic cells and macrophages when induced by HIV infection. 1725 is involved in T cell activation required for HIV replication. Therefore, antagonizing 1725 would inhibit HIV replication.

[0020] Due to 1725 mRNA expression in macrophages, PBMC, tonsil and lymph node, along with its functional role, modulators of 1725 activity would be useful in treating AIDS and HIV-related disorders. 1725 polypeptides of the present invention are useful to screen for modulators of 1725 activity.

Gene ID 311

[0021] The human 311 sequence (SEQ ID NO:5), known also as the nicotinic acid receptor (HM74A), is approximately 2051 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 61 to 1224 of SEQ ID NO:5, encodes a 387 amino acid protein (SEQ ID NO:6).

[0022] As assessed by TaqMan analysis, 311 mRNA was highly expressed in spleen, tonsil, lymph node and PBMC. 311 mRNA was induced by HIV infection of dendritic cells, dendritic cell/T cell co-cultures and macrophages.

[0023] 311 is the nicotinic acid receptor, HM74A (*JBC*, 2003, 278:9869-9874). Administration of nicotinic acid is used in the treatment of dyslipidemia which is believed to inhibit adipocyte lipolysis via the activation of a Gi-coupled receptor. Gi-coupled receptor stimulation results in the activation of MAP and JNK kinases which are involved in the production of cytokines and cell division. HIV replication requires T cell activation. Antagonizing 311 would result in decreased T cell activation and viral replication.

[0024] Due to 311 mRNA expression in the spleen, tonsil, lymph node and PBMC, along with its functional role, modulators of 311 activity would be useful in treating AIDS and HIV-related disorders. 311 polypeptides of the present invention are useful to screen for modulators of 311 activity.

Gene ID 837

[0025] The human 837 sequence (SEQ ID NO:7), known also as the alpha 7 subunit of the acetylcholine receptor, is approximately 2087 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 104 to 1612 of SEQ ID NO:7, encodes a 502 amino acid protein (SEQ ID NO:8).

[0026] As assessed by TaqMan analysis, 837 mRNA was highly expressed in peripheral blood lymphocytes (PBL) and tonsil. 837 mRNA was induced by HIV infection of CD4+ T cells, thymocytes, dendritic cells, dendritic cell/CD4+ T co-cultures.

[0027] 837 is required for an anti-inflammatory response that inhibits TNFα secretion by macrophages (*Nature*, May 2000, 405(6785):458-462). 837 knockouts display elevated levels of TNFα. TNFα is secreted by macrophages, which enhances HIV replication in a paracrine fashion. Agonizing 837 will reduce the level of TNFα secreted by macrophages, resulting in reduced HIV replication.

[0028] Due to 837 mRNA expression in the PBL and tonsil, along with its functional role, modulators of 837 activity would be useful in treating AIDS and HIV-related disorders. 837 polypeptides of the present invention are useful to screen for modulators of 837 activity.

Gene ID 58305

[0029] The human 58305 sequence (SEQ ID NO:9), known also as vesicular inhibitory amino acid transporter (GABA and glycine) (hVIAAT), is approximately 2585 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 248 to 1825 of SEQ ID NO:9, encodes a 525 amino acid protein (SEQ ID NO:10).

[0030] As assessed by transcriptional profiling, 58305 mRNA expression was up regulated in PBMCs of SIV infected rhesus macaque monkeys. This was confirmed by RT-PCR.

[0031] T lymphocyte activation is required for viral replication. Activated T cells are highly metabolically active and undergo multiple rounds of cell division. Each cell division requires a doubling of cellular proteins, requiring increased cellular uptake of amino acids for protein synthesis. During HIV replication up to thirty percent of total cellular mRNA can be viral transcripts resulting in high levels of viral protein synthesis. Therefore, inhibition of 58305 will inhibit T cell activation and viral protein synthesis resulting in decreased viral replication.

[0032] Due to 58305 mRNA expression in HIV-infected T-cells, along with its functional role, modulators of 58305 activity would be useful in treating AIDS and HIV-related disorders. 58305 polypeptides of the present invention are useful to screen for modulators of 58305 activity.

Gene ID 156

[0033] The human 156 sequence (SEQ ID NO:11), known also as formyl peptide receptor-like 2 (FPRL2), is approximately 1062 nucleotides long. The coding sequence, located at about nucleic acid 1 to 1062 of SEQ ID NO:11, encodes a 353 amino acid protein (SEQ ID NO:12).

[0034] As assessed by transcriptional profiling, 156 mRNA expression was up regulated in dendritic cell/CD4+ T cell cocultures. TaqMan analysis indicated that 156 mRNA was expressed at relatively low levels in most tissues and was expressed at higher

levels in dendritic cell/CD4+ T cells and macrophages. 156 mRNA was also up regulated in HIV infected macrophages, primary CD4+ T lymphocytes, thymocytes and T cells.

[0035] Immature dendritic cells (iDC) respond chemotactically and by Ca(2+) mobilization to N-formyl-Met-Leu-Phe and a recently identified synthetic peptide Trp-Lys-Tyr-Met-Val-D-Met (WKYMVm; SEQ ID NO:53), whereas mature dendritic cells (mDC) derived from the same donor only respond to WKYMVm. Furthermore, iDC and mDC express FPRL2 mRNA and protein. As mDC do not express any other members of the human FPR subfamily, FPRL2 expressed by DC must be functional and mediate the effect of WKYMVm on DC (*J Leukoc Biol,* 2002 Sep;72(3):598-607).

[0036] Stimulation of GPCRs, including 156 which is Gi linked, leads to T cell activation and proliferation. HIV replication requires T cell activation. FPRL2, expressed in myeloid DC, maintains its maturation, suggesting that the interaction of FPRL2 and its endogenous ligand(s) may be involved in regulating DC trafficking during antigen uptake and processing in the periphery as well as the T cell-stimulating phase of immune responses. Therefore antagonizing 156 would provide a means to inhibit T cell activation and HIV replication.

[0037] Due to 156 mRNA expression in T lymphocytes and T cell lines, along with its functional role, modulators of 156 activity would be useful in treating AIDS and HIV-related disorders. 156 polypeptides of the present invention are useful to screen for modulators of 156 activity.

Gene ID 14175

[0038] The human 14175 sequence (SEQ ID NO:13), known also as serine/threonine protein kinase 10 or lymphocyte-oriented kinase (LOK), is approximately 4221 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 51 to 2957 of SEQ ID NO:13, encodes a 968 amino acid protein (SEQ ID NO:14).

[0039] As assessed by TaqMan analysis, 14175 mRNA expression was detected in lymphocytes of SIV infected rhesus macaques. TaqMan analysis of an organ recital panel indicated 14175 mRNA was highly expressed in PBMCs compared to other organs. TaqMan analysis of an inflammation panel also confirmed expression of 14175 mRNA in lymphocytes and monocytes.

[0040] T lymphocyte activation is required for viral replication. A number of kinases are involved in T cell activation following stimulation through the T cell receptor.

14175 is a new and unique member of the STE20 family with serine/threonine kinase activity and its expression is restricted mostly to lymphoid cells (*Immunogenetics*, 1999 May;49(5):369-75). 14175 is involved in mitogen-activated protein (MAP) kinase cascades, which is induced by viral replication. 14175 gene expression is slightly induced in response to T cell activation and HIV infection, suggesting that 14175 is required for viral replication. Therefore, antagonizing 14175 will inhibit T cell activation and viral replication.

[0041] Due to 14175 mRNA expression in lymphocytes and PBMCs, along with its functional role, modulators of 14175 activity would be useful in treating AIDS and HIV-related disorders. 14175 polypeptides of the present invention are useful to screen for modulators of 14175 activity.

Gene ID 50352

[0042] The human 50352 sequence (SEQ ID NO:15), known also as a ubiquitin transferase, is approximately 3513 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 82 to 3150 of SEQ ID NO:15, encodes a 1022 amino acid protein (SEQ ID NO:16).

[0043] As assessed by TaqMan analysis, 50352 mRNA expression was up regulated in HIV infected dendritic cell/CD4 + T cell cocultures. TaqMan analysis of organ recital panels indicated high expression of 50352 mRNA in PBMCs and macrophages. RT-PCR of HIV infected PBMCs, monocytes and the T cell line CEM indicated increased expression of 50352 mRNA.

[0044] Ubiquitin transferases catalyze the addition of ubiquitin to cellular proteins resulting in degradation by the proteosome. Many molecules necessary for transcription of the HIV genome require ubiquitin transferases for regulation, including NFkB. T lymphocyte activation also requires ubiquitin transferases for regulation which is required for viral replication. 50352 is required for processing of HIV Gag proteins. Ubiquitination of cellular proteins precedes degradation or processing of proteins by 50352. Therefore, inhibition of 50352 inhibits T cell activation and viral replication.

[0045] Due to 50352 mRNA expression in dendritic cell/CD4 + T cell cocultures and T cell lines, along with its functional role, modulators of 50352 activity would be useful in treating AIDS and HIV-related disorders. 50352 polypeptides of the present invention are useful to screen for modulators of 50352 activity.

Gene ID 32678

[0046] The human 32678 sequence (SEQ ID NO:17), known also as an acid-sensing channel (ASIC1), is approximately 3923 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 230 to 1954 of SEQ ID NO:17, encodes a 574 amino acid protein (SEQ ID NO:18).

[0047] As assessed by transcriptional profiling, 32678 mRNA expression was up regulated in HIV infected thymocytes and the T cell line C8166. TaqMan analysis confirmed increased expression of 32678 mRNA in HIV infected primary macrophages at multiple time points. 32678 mRNA expression was dramatically increased at the peak of infection of two T lymphocyte cell lines, H9 and C8166.

[0048] 32678 or ASIC1 is an acid-sensing channel that is permeable to calcium and will cause depolarization of the cell membrane. Depolarization of the cell membrane will open voltage sensitive calcium channels (VSCC's) leading to increased accumulation of intracellular calcium. (*Nature*, 1997 Mar 13;386(6621):173-7). Calcium is an important intracellular messenger that is released from intracellular storage compartments and from plasma membrane Ca++ channels following the generation of inositol triphosphate (InsP3). InsP3 is involved in signaling through the T cell receptor (TCR)/CD3 complex resulting in T cell activation (*Cell*, 1989 Oct 6;59(1):15-20). T cell activation through the TCR/CD3 complex is required for HIV replication in T lymphocytes. Therefore, antagonizing 32678 may inhibit signaling through the TCR/CD3 complex resulting in decreased T cell activation and HIV replication.

[0049] Due to 32678 mRNA expression in HIV-infected T cells, along with its functional role, modulators of 32678 activity would be useful in treating AIDS and HIV-related disorders. 32678 polypeptides of the present invention are useful to screen for modulators of 32678 activity.

Gene ID 5560

[0050] The human 5560 sequence (SEQ ID NO:19), known also as aspartyl protease 3, is approximately 1373 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 31 to 1373 of SEQ ID NO:19, encodes a 448 amino acid protein (SEQ ID NO:20).

[0051] As assessed by transcriptional profiling, 5560 mRNA expression increased in HIV infected thymocytes and primary CD4+ T cells. 5560 mRNA expression was highly restricted to T cells and lymphoid tissue and is further induced upon T cell activation and HIV infection. Increased 5560 mRNA expression in HIV infected thymocytes, CD4+ T cells, dendritic cells, monocytes and the T cell line ACH2 was confirmed by TaqMan analysis.

[0052] 5560 is an aspartyl protease. 5560 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. Some cellular proteases are known to cleave the HIV gap-pol protein precursor. Inhibition of 5560 may inhibit HIV replication.

[0053] Due to 5560 mRNA expression in HIV-infected thymocytes and T cells, along with its functional role, modulators of 5560 activity would be useful in treating AIDS and HIV-related disorders. 5560 polypeptides of the present invention are useful to screen for modulators of 5560 activity.

Gene ID 7240

[0054] The human 7240 sequence (SEQ ID NO:21), known also as aldehyde dehydrogenase 1 (ALDH1) or retinal dehydrogenase 1, is approximately 1506 nucleotides long. The coding sequence, located at about nucleic acid 1 to 1506 of SEQ ID NO:21, encodes a 501 amino acid protein (SEQ ID NO:22).

[0055] As assessed by transcriptional profiling, 7240 mRNA expression was up regulated in HIV infected dendritic cell/CD4+ T cell cocultures (DC/TC). RT-PCR confirmed expression in HIV infected DC/TC, macrophages and the T cell line ACH2.

[0056] Metabolism of retinaldehyde to retinoic acid (RA) is tissue-restricted and ALDH1 is expressed at high levels in DC/TC, macrophages and the T cell line ACH2. ALDH1 is required to metabolize retinol to RA to initiate retinoid signaling. (*Chem Biol Interact*, 2003 Feb 1;143-144:201-10). Retinoic acid receptor alpha (RXRα) stimulates transcription from the HIV LTR by binding to the nuclear receptor-responsive element in the presence of RA. Inhibitors of ALDH1 would prevent the conversion of retinaldehyde to RA and prevent RXRα stimulated transcription from the HIV LTR resulting in decreased HIV replication. An FDA approved small molecule inhibitor of ALDH1 exists (disulfiram). (*J. Biol. Chem.*, Feb 1994; 269:5944 – 5951).

[0057] Due to 7240 mRNA expression in HIV infected DC/TC, along with its functional role, modulators of 7240 activity would be useful in treating AIDS and HIV-

related disorders. 7240 polypeptides of the present invention are useful to screen for modulators of 7240 activity.

Gene ID 8865

[0058] The human 8865 sequence (SEQ ID NO:23), known also as transglutaminase 2 (TGase), is approximately 3257 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 136 to 2199 of SEQ ID NO:23, encodes a 687 amino acid protein (SEQ ID NO:24).

[0059] As assessed by transcriptional profiling, 8865 mRNA expression was deregulated in gene arrays of HIV infection of dendritic cell/T cell cocultures (DC/TC). RT-PCR confirms expression of 8865 mRNA in HIV infected T cell lines, macrophages, primary CD4+ cells and DC/TC.

[0060] TGase cross links polyamines to target proteins, and is regulated by the GTP binding activity of TGase. (*J. Biol. Chem.*, January 3, 2003, 278(1):391-399). The transamidation reaction of TGase has been implicated in a number of biological processes including cellular differentiation, and apoptosis. Mitogens, tumor promoters, and cell differentiation inducing agents trigger an intracellular signaling cascade, which involves Ras and Rho GTPases and leads to activation of mitogen-activated protein (MAP) kinases. HIV is also known to induce cellular signaling pathways including MAP kinases. Retinoic acid (RA) promotes activation of TGase and *in vivo* transamidation of RhoA. RhoA binds/activates RhoA-associated kinase-2 (ROCK-2), a downstream target and an effector of GTP-bound RhoA which promotes activation of MAP/ERK kinases leading to regulation of nuclear events. Inhibition of TGase would prevent the Rho GTPase activation of MAP/ERK kinases resulting in decreased HIV replication.

[0061] Due to 8865 mRNA expression in HIV infected T cell lines, macrophages, primary CD4+ cells and DC/TC, along with its functional role, modulators of 8865 activity would be useful in treating AIDS and HIV-related disorders. 8865 polypeptides of the present invention are useful to screen for modulators of 8865 activity.

Gene ID 12396

[0062] The human 12396 sequence (SEQ ID NO:25), known also as the GPCR GPR41, is approximately 1061 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 11 to 1051 of SEQ ID NO:25, encodes a 346 amino acid protein (SEQ ID NO:26).

[0063] As assessed by transcriptional profiling, 12396 mRNA expression was restricted primarily to leukocytes. RT-PCR indicated increased 12396 mRNA expression in HIV infected macrophages, dendritic cells, the T cell line ACH2 and in T cells stimulated with antibodies to CD3.

[0064] Propionate was the most potent agonist for GPR41. The receptor is coupled to Inositol 1,4,5-trisphosphate (IP3) formation, intracellular Ca2+ release, ERK1/2 activation and inhibition of cyclic adenosine monophosphate (cAMP) accumulation. GPR41 is coupled exclusively though the Pertussis toxin-sensitive Gi/o family (*J. Biol. Chem.* 2003 Apr 23; [epub ahead of print]). HIV replication requires T cell activation which requires cAMP accumulation. Agonizing this receptor would result in the inhibition of cAMP accumulation and decreased HIV replication which would be beneficial in the treatment of HIV infection.

[0065] Due to 12396 mRNA expression in HIV infected macrophages, dendritic cells, the T cell line ACH2 and in T cells stimulated with antibodies to CD3, along with its functional role, modulators of 12396 activity would be useful in treating AIDS and HIV-related disorders. 12396 polypeptides of the present invention are useful to screen for modulators of 12396 activity.

Gene ID 12397

[0066] The human 12397 sequence (SEQ ID NO:27), known also as GPCR GPR43, is approximately 1013 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 11 to 1003 of SEQ ID NO:27, encodes a 330 amino acid protein (SEQ ID NO:28).

[0067] As assessed by transcriptional profiling, 12397 mRNA expression was restricted primarily to leukocytes. RT-PCR indicated increased 12397 mRNA expression in HIV infected macrophages, dendritic cells and the T cell line ACH2.

[0068] Propionate was the most potent agonist for GPR43. The receptor is coupled to IP3 formation, intracellular Ca2+ release, ERK1/2 activation and increased cAMP accumulation. GPR43 displayed a dual coupling through Gi/o and Pertussis toxin-insensitive Gq protein families. GPCR 43 is believed to be involved in the induction of proinflammatory immune responses. (*J. Biol. Chem.* 2003 Apr 23; [epub ahead of print]). HIV infection is characterized by high level immune activation which correlates with disease progression. Therapies targeting immune activation have shown efficacy in the

treatment of HIV in humans. Antagonizing this receptor would prevent activation of the immune response by leukocytes and inhibit HIV infection.

[0069] Due to 12397 mRNA expression in HIV infected macrophages, dendritic cells and the T cell line ACH2, along with its functional role, modulators of 12397 activity would be useful in treating AIDS and HIV-related disorders. 12397 polypeptides of the present invention are useful to screen for modulators of 12397 activity.

Gene ID 13644

[0070] The human 13644 sequence (SEQ ID NO:29), known also as monocarboxylate transporter 4 (MCT 4), is approximately 1982 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 63 to 1460 of SEQ ID NO:29, encodes a 465 amino acid protein (SEQ ID NO:30).

[0071] As assessed by transcriptional profiling, 13644 mRNA was highly expressed in T cells and macrophages. 13644 mRNA was expressed at higher levels in HIV permissive macrophages when compared to nonpermissive macrophages. HIV infection induced 13644 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0072] MCT4 is most evident in white muscle and other cells with a high glycolytic rate, such as tumor cells and white blood cells, suggesting it is expressed where lactic acid efflux predominates (*Biochem. J.*, 1999, 343:281–299). T cell activation is required for efficient HIV replication. Activated T cells generate the majority of energy needs via glycolysis. Inhibition of MCT4 would lower the level of T cell activation by inhibition of lactic acid efflux, resulting in inhibition of HIV replication (*Biochem. J.*, 1999, 343:281–299).

[0073] Due to 13644 mRNA expression in HIV infected macrophages, dendritic cells and T cells, along with its functional role, modulators of 13644 activity would be useful in treating AIDS and HIV-related disorders. 13644 polypeptides of the present invention are useful to screen for modulators of 13644 activity.

Gene ID 19938

[0074] The human 19938 sequence (SEQ ID NO:31), known also as kynurenine 3-hydroxylase, is approximately 1999 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 53 to 1513 of SEQ ID NO:31, encodes a 486 amino acid protein (SEQ ID NO:32).

[0075] As assessed by transcriptional profiling, 19938 mRNA expression was up regulated in HIV infected dendritic cell/CD4+ cell co-cultures (DC/TC). RT-PCR analysis confirmed expression in DC, DC/TC and monocytes.

[0076] IDO (Indeolamine 2,3-dioxygenase) catalyzes the degradation of tryptophan to kynurenine and subsequent catabolic byproducts. IDO is implicated in the induction of T cell tolerance. Local decreases in availability of tryptophan and the presence of its catabolic byproducts inhibit T cell proliferation and may induce apoptotic death (*Nature Immunology,* 2002, 3:1056-1057). 19938 converts kynurenine to hydroxykynurenine. 19938 mRNA expression is induced in HIV infected DC and DC/TC.

[0077] The induction of this enzyme may have a direct effect of HIV infection. T cell tolerance is seen in patients with HIV infection. Increased levels of apoptosis are also seen in human and primate models of pathogenic HIV and SIV infection. The reduction in tryptophan levels and the accumulation of kynurenine may be responsible for increased T cell tolerance as well as increased levels of apoptosis in HIV infected and noninfected T lymphocytes. Therefore, inhibition of 19938 may prevent T cell tolerance and the increased apoptosis of T lymphocytes seen in patients with HIV infection.

[0078] Due to 19938 mRNA expression in HIV infected dendritic cell/CD4+ cell co-cultures (DC/TC), along with its functional role, modulators of 19938 activity would be useful in treating AIDS and HIV-related disorders. 19938 polypeptides of the present invention are useful to screen for modulators of 19938 activity.

Gene ID 2077

[0079] The human 2077 sequence (SEQ ID NO:33), known also as glomerular epithelial protein 1 (GLEPP1) or protein-tyrosine-phosphatase receptor type O precursor, is approximately 5415 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 173 to 3739 of SEQ ID NO:33, encodes an 1188 amino acid protein (SEQ ID NO:34).

[0080] As assessed by transcriptional profiling, 2077 mRNA was highly expressed in dendritic cells and macrophages. HIV infection induced 2077 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0081] 2077 is induced by HIV infection suggesting a role in viral replication. 2077 may dephosphorylate cellular proteins involved in inhibition of replication. If this phosphatase enhances viral replication, then antagonizing 2077 would inhibit HIV replication.

[0082] Due to 2077 mRNA expression in HIV infected macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC), along with its functional role, modulators of 2077 activity would be useful in treating AIDS and HIV-related disorders. 2077 polypeptides of the present invention are useful to screen for modulators of 2077 activity.

Gene ID 1735

[0083] The human 1735 sequence (SEQ ID NO:35), known also as matrix metalloproteinase-9 (MMP-9), is approximately 2373 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 6 to 2129 of SEQ ID NO:35, encodes a 707 amino acid protein (SEQ ID NO:36).

[0084] As assessed by transcriptional profiling, 1735 mRNA expression increased in HIV infected macrophages and dendritic cells. 1735 mRNA expression was highly restricted to macrophages and dendritic cells and was further induced upon HIV infection. Increased 1735 mRNA expression in HIV infected macrophages and in dendritic cells was confirmed by TaqMan analysis.

[0085] 1735 is a matrix metalloprotease. 1735 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. MMP9 is associated with immune activation and may affect leukocyte entry into the brain. (*J Virol.* 2001 Jul; 75(14):6572-83). Inhibition of MMP-9 may result in decreased viral replication as well as decreased HIV associated neuropathy.

[0086] Due to 1735 mRNA expression in HIV infected macrophages and dendritic cells, along with its functional role, modulators of 1735 activity would be useful in treating AIDS and HIV-related disorders. 1735 polypeptides of the present invention are useful to screen for modulators of 1735 activity.

Gene ID 1786

[0087] The human 1786 sequence (SEQ ID NO:37), known also as granzyme B, is approximately 934 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 8 to751 of SEQ ID NO:37, encodes a 247 amino acid protein (SEQ ID NO:38).

[0088] As assessed by transcriptional profiling, 1786 mRNA expression increased in HIV infected thymocytes and primary CD4+ T cells as well as in a Jurkat T cell clone highly permissive to infection. 1786 mRNA expression was highly restricted to T cells

and lymphoid tissue and was further induced upon T cell activation and HIV infection. Increased 1786 mRNA expression in HIV infected thymocytes, CD4+ T cells, and in the Jurkat T cell line was confirmed by TaqMan analysis.

[0089] Granzyme B is a T cell- and natural killer cell-specific trypsin-like serine protease that is released from effector cells during cytotoxic cell killing. Granzyme B is essential for the induction of DNA fragmentation and apoptosis in target cells. Granzyme B is found in the blood of normal individuals and at increased levels in patients with rheumatoid arthritis and acute EBV and HIV infection suggesting that granzymes have additional biological effects. Granzyme B is known to induce IL-6 and IL-8 production in fibroblasts and stimulates IL-6, IL-8 and TNF-alpha from monocytes. (*J Immunol.* 1998 Apr 1; 160(7):3610-3616). Proinflamatory cytokines contribute to increased levels of immune activation and viral replication, therefore inhibition of Granzyme B should inhibit HIV replication.

[0090] Due to 1786 mRNA expression in HIV infected thymocytes, CD4+ T cells, and in the Jurkat T cell line, along with its functional role, modulators of 1786 activity would be useful in treating AIDS and HIV-related disorders. 1786 polypeptides of the present invention are useful to screen for modulators of 1786 activity.

Gene ID 10220

[0091] The human 10220 sequence (SEQ ID NO:39), known also as ionotropic purinergic receptor P2X7, is approximately 1853 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 27 to 1814 of SEQ ID NO:39, encodes a 595 amino acid protein (SEQ ID NO:40).

[0092] 10220 was identified in a transcriptional profile of HIV infected monocytes. It was expressed in most tissues and was expressed at higher levels in monocytes, dendritic cells, thymocytes, T lymphocytes and macrophages. 10220 mRNA expression was up regulated following HIV infection in macrophages as confirmed by RT-PCR.

[0093] P2X7 is a human purinoceptor 7 (ATP receptor) which facilitates cation channel activation and secretion of IL-1beta from LPS-primed macrophages (*J. Immunol.* 2003 Jun 1; 170(11):5728-38). HIV replication in macrophages stimulates IL-1 production in vivo and in vitro which acts in an autocrine and paracrine manner to enhance HIV replication in T cells and monocytes. Antibodies to IL-1 inhibit the enhanced HIV

replication due to IL-1 production in vitro. P2X7 knockout mice are healthy and fertile. Absence of the P2X7R thus leads to an inability of peritoneal macrophages to release IL-1 in response to ATP. (*J. Biol. Chem.*, January 5, 2001; 276(1):125-132). Inhibition of P2X7 dependent IL-1 production would decrease HIV replication and would not have deleterious effects as demonstrated by the knockout mice.

[0094] Due to 10220 mRNA expression in HIV infected monocytes and macrophages, along with its functional role, modulators of 10220 activity would be useful in treating AIDS and HIV-related disorders. 10220 polypeptides of the present invention are useful to screen for modulators of 10220 activity.

Gene ID 17822

[0095] The human 17822 sequence (SEQ ID NO:41), a dipeptidase similar to microsomal dipeptidase precursor 1 (MDP1), is approximately 1700 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 125 to1585 of SEQ ID NO:41, encodes a 486 amino acid protein (SEQ ID NO:42).

[0096] As assessed by TaqMan analysis, 17822 mRNA was highly expressed in dendritic cells and macrophages. 17822 mRNA expression was induced to higher levels in HIV permissive vs. nonpermissive macrophages. HIV infection induced 17822 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0097] 17822 is a membrane-bound dipeptidase. 17822 catalyzes the conversion of leukotriene D4 (LTD4) to leukotriene E4 (LTE4). (*The FASEB Journal.* 2003; 17:1313-1315). 17822 may also participate in immune/inflammatory processes involving leukotrienes which are elevated in patients with asthma and may play a role in pathogenesis. Proinflammatory molecules enhance HIV infection and it is possible that LTE4 may enhance replication, therefore inhibition of 17822 should inhibit viral replication.

[0098] Due to 17822 mRNA expression in HIV infected macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC), along with its functional role, modulators of 17822 activity would be useful in treating AIDS and HIV-related disorders. 17822 polypeptides of the present invention are useful to screen for modulators of 17822 activity.

Gene ID 33945

[0099] The human 33945 sequence (SEQ ID NO:43), known as UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 12 (GalNAc-T12), is approximately 2850 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 81 to 1826 of SEQ ID NO:43, encodes a 581 amino acid protein (SEQ ID NO:44).

[0100] 33945 was identified by transcriptional profiling of HIV infected monocytes. 33945 mRNA was highly expressed in T cells, dendritic cells and macrophages and was further induced upon HIV infection of monocytes, as confirmed by TaqMan analysis.

[0101] GalNAc-T12 is involved in O-linked glycosylation of many substrates including the V3 loop of HIV envelope. (*FEBS Lett.*, 2002 Jul 31; 524(1-3):211-8). 33945 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. Glycosylation of the HIV envelope is required for infectivity. Inhibitors of 33945 would inhibit the infectivity of HIV by preventing O-linked glycosylation of the V3 loop of HIV envelope.

[0102] Due to 33945 mRNA expression in HIV infected monocytes, along with its functional role, modulators of 33945 activity would be useful in treating AIDS and HIV-related disorders. 33945 polypeptides of the present invention are useful to screen for modulators of 33945 activity.

Gene ID 43748

[0103] The human 43748 sequence (SEQ ID NO:45), known also as aquaporin 9 (AQP9), is approximately 2890 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 229 to 1116 of SEQ ID NO:45, encodes a 295 amino acid protein (SEQ ID NO:46).

[0104] As assessed by TaqMan analysis, 43748 mRNA was highly expressed in dendritic cells and macrophages. 43748 mRNA expression was increased in HIV permissive vs. nonpermissive macrophages. HIV infection induced 43748 mRNA expression in macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC).

[0105] AQP9 is most evident in white muscle and other cells with a high glycolytic rate, such as tumor cells and white blood cells, suggesting it is expressed where lactic acid efflux predominates. T cell activation is required for efficient HIV replication. Activated T cells generate the majority of their energy needs via glycolysis. AQP9 is most predominant in white blood cells and it transports glycerol and urea at physiological pH.

(*Proc Natl Acad Sci USA*, 2003 Mar 4; 100(5):2945-50.; E pub 2003 Feb 19). Inhibition of AQP9 would lower the level of T cell metabolic activity by inhibition of transport of glycerol and urea, resulting in inhibition of HIV replication.

[0106] Due to 43748 mRNA expression in HIV infected macrophages, dendritic cells (DC) and dendritic cell/T cell cocultures (DC/TC), along with its functional role, modulators of 43748 activity would be useful in treating AIDS and HIV-related disorders. 43748 polypeptides of the present invention are useful to screen for modulators of 43748 activity.

Gene ID 47161

[0107] The human 47161 sequence (SEQ ID NO:47), known also as N-acetylgalactosaminyltransferase 6 (GalNAc-T6), is approximately 1869 nucleotides long. The coding sequence, located at about nucleic acid 1 to 1869 of SEQ ID NO:47, encodes a 622 amino acid protein (SEQ ID NO:48).

[0108] 47161 was identified by transcriptional profiling of HIV infected monocytes. 47161 mRNA expression was very restricted and was highly expressed in T cells, dendritic cells and macrophages and is further induced upon HIV infection of monocytes, as confirmed by TaqMan analysis.

[0109] GalNAc-T6 is involved in O-linked glycosylation of many substrates including the V3 loop of HIV envelope. (J Biol Chem., 1999 Sep 3; 274(36):25362-70). 47161 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. Glycosylation of the HIV envelope is required for infectivity. Inhibitors of 47161 would inhibit the infectivity of HIV by preventing O-linked glycosylation of the V3 loop of HIV envelope.

[0110] Due to 47161 mRNA expression in HIV infected monocytes, along with its functional role, modulators of 47161 activity would be useful in treating AIDS and HIV-related disorders. 47161 polypeptides of the present invention are useful to screen for modulators of 47161 activity.

Gene ID 81982

[0111] The human 81982 sequence (SEQ ID NO:49), known also as "probable serine protease HTRA4 precursor", is approximately 1544 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 87 to 1517 of SEQ ID NO:49, encodes a 476 amino acid protein (SEQ ID NO:50).

[0112] As assessed by transcriptional profiling, 81982 mRNA expression was increased in HIV infected macrophages and dendritic cells. 81982 mRNA expression was highly restricted to macrophages and dendritic cells and was further induced upon HIV infection. Increased 81982 mRNA expression in HIV infected macrophages and dendritic cells was confirmed by TaqMan analysis.

[0113] 81982 is a serine protease. 81982 is greatly induced following HIV infection suggesting that this enzyme is required for efficient viral replication. 5-hydroxytryptamine (serotonin) receptor 4 (HTr4) is in the secretory pathway and is involved in degrading damaged proteins and signal peptides found on HIV proteins. High level protein synthesis occurs during HIV replication. These proteins accumulate inside the cell membrane and assemble to form virions. In vivo, aggregate formation is a highly favorable process due to the extremely high intracellular protein concentrations. HTr4 is a protease-chaperone heat shock protein that prevents aggregate formation (*Molecular Cell,* Sept. 2002; 10:443-455). Inhibition of this enzyme may interfere with virion protein assembly, maturation and release of viral particles.

[0114] Due to 81982 mRNA expression in HIV infected macrophages and dendritic cells, along with its functional role, modulators of 81982 activity would be useful in treating AIDS and HIV-related disorders. 81982 polypeptides of the present invention are useful to screen for modulators of 81982 activity.

Gene ID 46777

[0115] The human 46777 sequence (SEQ ID NO:51), known also as disintegrin-protease, is approximately 2187 nucleotides long including untranslated regions. The coding sequence, located at about nucleic acid 61 to 1473 of SEQ ID NO:51, encodes a 470 amino acid protein (SEQ ID NO:52).

[0116] As assessed by transcriptional profiling, 46777 mRNA expression levels increased in HIV infected thymocytes and primary DC/TC (dendritic cell/T cell cocultures) compared to non-infected samples. 46777 tissue expression was highly restricted to T cells and lymphoid tissue and was further induced upon T cell activation and HIV infection. TaqMan experiments additionally confirmed that 46777 mRNA expression was increased in HIV infected thymocytes, dendritic cells, and monocytes.

[0117] 46777 is a protease which is greatly induced following HIV infection, suggesting that this enzyme is required for efficient viral replication. Some cellular

proteases are known to cleave the HIV gap-pol protein precursor. Therefore, inhibition of 46777 should inhibit HIV replication.

[0118] Therefore, based on the specific expression and regulation of 46777 in HIV infected tissues and cell types, such thymocytes and T cells, modulators of 46777 activity would be useful in treating AIDS or an HIV-related disorder. 46777 polypeptides of the present invention would be useful in screening for modulators of 46777 activity.

[0119] Various aspects of the invention are described in further detail in the following subsections:

I. Screening Assays:

[0120] The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules (organic or inorganic) or other drugs) which bind to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, have a stimulatory or inhibitory effect on, for example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate. Compounds identified using the assays described herein may be useful for treating AIDS or an HIV-related disorder.

[0121] These assays are designed to identify compounds that bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, bind to other intracellular or extracellular proteins that interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, and interfere with the interaction of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with other intercellular or extracellular proteins. For example, in the case of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, which is a transmembrane receptor-type protein, such techniques can identify ligands for such a receptor. A 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein ligand or substrate can, for example, be used to ameliorate at least one symptom of AIDS or an HIV-related disorder. Such compounds may include, but are not limited to peptides, antibodies, or small organic or inorganic compounds. Such compounds may also include other cellular proteins.

[0122] Compounds identified via assays such as those described herein may be useful, for example, for treating AIDS or an HIV-related disorder. In instances whereby AIDS or an HIV-related disorder results from an overall lower level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression and/or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein in a cell or tissue, compounds that interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein may include compounds which accentuate or amplify the activity of the bound 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Such compounds would bring about an effective increase in the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity, thus ameliorating symptoms.

[0123] In other instances, mutations within the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene may cause aberrant types or excessive amounts of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins to be made which have a deleterious effect that leads to AIDS or an HIV-related disorder. Similarly, physiological conditions may cause an excessive increase in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression leading to AIDS or an HIV-related disorder. In such cases, compounds that bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein may be identified that inhibit the activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Assays for testing the effectiveness of compounds identified by techniques such as those described in this section are discussed herein.

[0124] In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution-phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

[0125] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

[0126] Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra.*).

[0127] In one embodiment, an assay is a cell-based assay in which a cell which expresses a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate 9145, 1725, 311, 837, 58305,

156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is determined. Determining the ability of the test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity can be accomplished by monitoring, for example, intracellular calcium, IP_3, cAMP, or diacylglycerol concentration, the phosphorylation profile of intracellular proteins, cell proliferation and/or migration, gene expression of, for example, cell surface adhesion molecules or genes associated with AIDS or an HIV-related disorder, or the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -regulated transcription factor. The cell can be of mammalian origin, *e.g.*, a neural cell. In one embodiment, compounds that interact with a receptor domain can be screened for their ability to function as ligands, *i.e.*, to bind to the receptor and modulate a signal transduction pathway. Identification of ligands, and measuring the activity of the ligand-receptor complex, leads to the identification of modulators (*e.g.*, antagonists) of this interaction. Such modulators may be useful in the treatment of AIDS or an HIV-related disorder.

[0128] The ability of the test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding to a substrate or to bind to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can also be determined. Determining the ability of the test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding to a substrate can be accomplished, for example, by coupling the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate with a radioisotope or enzymatic label such that binding of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be determined by

detecting the labeled 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate in a complex. 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 could also be coupled with a radioisotope or enzymatic label to monitor the ability of a test compound to modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate in a complex. Determining the ability of the test compound to bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be determined by detecting the labeled 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 compound in a complex. For example, compounds (*e.g.*, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ligands or substrates) can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Compounds can further be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

[0129] It is also within the scope of this invention to determine the ability of a compound (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ligand or substrate) to interact with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 without the labeling of any of

the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 without the labeling of either the compound or the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 (McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 .

[0130] In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate) with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule. Determining the ability of the test compound to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be accomplished, for example, by determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to or interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule.

[0131] Determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a biologically active fragment

thereof, to bind to or interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to or interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular Ca^{2+}, diacylglycerol, IP_3, cAMP), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a target-regulated cellular response (*e.g.*, gene expression).

[0132] In yet another embodiment, an assay of the present invention is a cell-free assay in which a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof, is contacted with a test compound and the ability of the test compound to bind to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is determined. Preferred biologically active portions of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins to be used in assays of the present invention include fragments which participate in interactions with non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecules, *e.g.*, fragments with high surface probability scores. Binding of the test compound to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting

the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof with a known compound which binds 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, wherein determining the ability of the test compound to interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein comprises determining the ability of the test compound to preferentially bind to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or biologically active portion thereof as compared to the known compound. Compounds that modulate the interaction of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 with a known target protein may be useful in regulating the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, especially a mutant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0133] In another embodiment, the assay is a cell-free assay in which a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822,

33945, 43748, 47161, 81982 or 46777 protein can be accomplished, for example, by determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule by one of the methods described above for determining direct binding. Determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to bind to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA) (Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[0134] In another embodiment, determining the ability of the test compound to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be accomplished by determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to further modulate the activity of a downstream effector of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

[0135] In yet another embodiment, the cell-free assay involves contacting a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or biologically active portion thereof with a known compound which binds the

9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, wherein determining the ability of the test compound to interact with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein comprises determining the ability of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to preferentially bind to or modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule.

[0136] In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, or interaction of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or

glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding or activity determined using standard techniques.

[0137] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecules but which do not interfere with binding of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to its target molecule can be derivatized to the wells of the plate, and unbound target or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above

for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or target molecule.

[0138] In another embodiment, modulators of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein in the cell is determined. The level of expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein in the presence of the candidate compound is compared to the level of expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression based on this comparison. For example, when expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein expression. Alternatively, when expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of

9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein expression. The level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein expression in the cells can be determined by methods described herein for detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or protein.

[0139] In yet another aspect of the invention, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ("9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding proteins" or "9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -bp") and are involved in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Such 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding proteins are also likely to be involved in the propagation of signals by the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 targets as, for example, downstream elements of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -mediated signaling

pathway. Alternatively, such 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding proteins are likely to be 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 inhibitors.

[0140] The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo,* forming a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0141] In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be confirmed *in vivo, e.g.*, in an animal such as an animal model for AIDS or an HIV-related disorder, as described herein.

[0142] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further

use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulating agent, an antisense 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -specific antibody, or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

[0143] Any of the compounds, including but not limited to compounds such as those identified in the foregoing assay systems, may be tested for the ability to ameliorate at least one symptom of AIDS or an HIV-related disorder. Cell-based and animal model-based assays for the identification of compounds exhibiting such an ability to ameliorate at least one symptom of AIDS or an HIV-related disorder are described herein.

[0144] In addition, animal-based models of AIDS or an HIV-related disorder, such as those described herein, may be used to identify compounds capable of treating AIDS or an HIV-related disorder. Such animal models may be used as test substrates for the identification of drugs, pharmaceuticals, therapies, and interventions which may be effective in treating AIDS or an HIV-related disorder. For example, animal models may be exposed to a compound, suspected of exhibiting an ability to treat AIDS or an HIV-related disorder, at a sufficient concentration and for a time sufficient to elicit such an amelioration of at least one symptom of AIDS or an HIV-related disorder in the exposed animals. The response of the animals to the exposure may be monitored by assessing the reversal of the symptoms of AIDS or an HIV-related disorder before and after treatment.

[0145] With regard to intervention, any treatments which reverse any aspect of a viral disorder (i.e. have an effect on AIDS or an HIV-related disorder) should be

considered as candidates for AIDS or an HIV-related disorder therapeutic intervention. Dosages of test agents may be determined by deriving dose-response curves.

[0146] Additionally, gene expression patterns may be utilized to assess the ability of a compound to ameliorate at least one symptom of AIDS or an HIV-related disorder. For example, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile", as used herein, includes the pattern of mRNA expression obtained for a given tissue or cell type under a given set of conditions. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR. In one embodiment, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences may be used as probes and/or PCR primers for the generation and corroboration of such gene expression profiles.

[0147] Gene expression profiles may be characterized for known states, either viral disease or normal, within the cell- and/or animal-based model systems. Subsequently, these known gene expression profiles may be compared to ascertain the effect a test compound has to modify such gene expression profiles, and to cause the profile to more closely resemble that of a more desirable profile.

[0148] For example, administration of a compound may cause the gene expression profile of AIDS or an HIV-related disorder disease model system to more closely resemble the control system. Administration of a compound may, alternatively, cause the gene expression profile of a control system to begin to mimic AIDS or an HIV-related disorder or AIDS or an HIV-related disease state. Such a compound may, for example, be used in further characterizing the compound of interest, or may be used in the generation of additional animal models.

II. Cell- and Animal-Based Model Systems

[0149] Described herein are cell- and animal-based systems which act as models for AIDS or an HIV-related disorder. These systems may be used in a variety of applications. For example, the cell- and animal-based model systems may be used to further characterize differentially expressed genes associated with AIDS or an HIV-related disorder, *e.g.*, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . In addition, animal- and cell-based assays may be used as part of screening strategies designed to identify compounds which are capable of ameliorating at least one symptom of AIDS or an HIV-related disorder, as described, below. Thus, the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions which may be effective in treating AIDS or an HIV-related disorder. Furthermore, such animal models may be used to determine the LD50 and the ED50 in animal subjects, and such data can be used to determine the *in vivo* efficacy of potential urological disorder treatments.

A. Animal-Based Systems

[0150] Animal-based model systems of urological disorder may include, but are not limited to, non-recombinant and engineered transgenic animals.

[0151] Non-recombinant animal models for AIDS or an HIV-related disorder may include, for example, genetic models.

[0152] Additionally, animal models exhibiting AIDS or an HIV-related disorder may be engineered by using, for example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences described above, in conjunction with techniques for producing transgenic animals that are well known to those of skill in the art. For example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences may be introduced into, and overexpressed in, the genome of the animal of interest, or, if endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences are present, they may either be overexpressed or, alternatively, be disrupted in order to underexpress or inactivate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865,

12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression.

[0153] The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences have been introduced into their genome or homologous recombinant animals in which endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences have been altered. Such animals are useful for studying the function and/or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 and for identifying and/or evaluating modulators of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

[0154] A transgenic animal used in the methods of the invention can be created by introducing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNA sequence can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, such as a mouse or rat 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, can be used as a transgene. Alternatively, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene homologue, such as another 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 family member, can be isolated based on hybridization to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNA sequences and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 transgene to direct expression of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods

are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 transgene in its genome and/or expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can further be bred to other transgenic animals carrying other transgenes.

[0155] To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene. The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene can be a human gene but more preferably, is a non-human homologue of a human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene. For example, a rat 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene can be used to construct a homologous recombination nucleic acid molecule, *e.g.*, a vector, suitable for altering an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in the mouse genome. In a preferred embodiment, the homologous recombination nucleic acid molecule is designed such that, upon homologous recombination, the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene is functionally disrupted

(*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the homologous recombination nucleic acid molecule can be designed such that, upon homologous recombination, the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein). In the homologous recombination nucleic acid molecule, the altered portion of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene to allow for homologous recombination to occur between the exogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene carried by the homologous recombination nucleic acid molecule and an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in a cell, *e.g.*, an embryonic stem cell. The additional flanking 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the homologous recombination nucleic acid molecule (see, *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The homologous recombination nucleic acid molecule is introduced into a cell, *e.g.*, an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene has homologously recombined with the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748,

47161, 81982 or 46777 gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells can then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination nucleic acid molecules, *e.g.*, vectors, or homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

[0156] In another embodiment, transgenic non-human animals for use in the methods of the invention can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

[0157] Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, *e.g.*, a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_o phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster

animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, *e.g.*, the somatic cell, is isolated.

[0158] The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 transgenic animals that express 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 peptide (detected immunocytochemically, using antibodies directed against 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 epitopes) at easily detectable levels should then be further evaluated to identify those animals which display a characteristic HIV-related disorder.

B. Cell-Based Systems

[0159] Cells that contain and express 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences which encode a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, and, further, exhibit cellular phenotypes associated AIDS or an HIV-related disorder, may be used to identify compounds that exhibit an effect on AIDS or an HIV-related disorder. Such cells may include non-recombinant monocyte cell lines, such as U937 (ATCC# CRL-1593), THP-1 (ATCC#TIB-202), and P388D1 (ATCC# TIB-63); endothelial cells such as human umbilical vein endothelial cells (HUVECs), human microvascular endothelial cells (HMVEC), and bovine aortic endothelial cells (BAECs); as well as generic mammalian cell lines such as HeLa cells and COS cells, *e.g.*, COS-7 (ATCC# CRL-1651), and T-cell or monocyte cell lines.. Further, such cells may include recombinant, transgenic cell lines. For example, the AIDS or an HIV-related disorder animal models of the invention, discussed above, may be used to generate cell lines, containing one or more cell types involved in AIDS or an HIV-related disorder, that can be used as cell culture models for this disorder. While primary cultures derived from the urological disorder model transgenic animals of the invention may be utilized, the generation of continuous cell lines

is preferred. For examples of techniques which may be used to derive a continuous cell line from the transgenic animals, see Small *et al.*, (1985) *Mol. Cell Biol.* 5:642-648.

[0160] Alternatively, cells of a cell type known to be involved in AIDS or an HIV-related disorder may be transfected with sequences capable of increasing or decreasing the amount of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression within the cell. For example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences may be introduced into, and overexpressed in, the genome of the cell of interest, or, if endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences are present, they may be either overexpressed or, alternatively disrupted in order to underexpress or inactivate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression.

[0161] In order to overexpress a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, the coding portion of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene may be ligated to a regulatory sequence which is capable of driving gene expression in the cell type of interest, *e.g.*, an endothelial cell. Such regulatory regions will be well known to those of skill in the art, and may be utilized in the absence of undue experimentation. Recombinant methods for expressing target genes are described above.

[0162] For underexpression of an endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequence, such a sequence may be isolated and engineered such that when reintroduced into the genome of the cell type of interest, the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 alleles will be inactivated. Preferably, the engineered 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence

is introduced via gene targeting such that the endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence is disrupted upon integration of the engineered 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence into the cell's genome. Transfection of host cells with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genes is discussed, above.

[0163] Cells treated with compounds or transfected with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genes can be examined for phenotypes associated with AIDS or an HIV-related disorder.

[0164] Transfection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid may be accomplished by using standard techniques (described in, for example, Ausubel (1989) *supra*). Transfected cells should be evaluated for the presence of the recombinant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences, for expression and accumulation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA, and for the presence of recombinant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein production. In instances wherein a decrease in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression is desired, standard techniques may be used to demonstrate whether a decrease in endogenous 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression and/or in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein production is achieved.

[0165] Also provided are cells or a purified preparation thereof, e.g., human cells, in which an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 is under the control of a regulatory sequence that does not normally control the expression of the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. The expression characteristics of an endogenous gene within a cell, e.g., a cell line or microorganism, can be modified by inserting a heterologous DNA regulatory element into the genome of the cell such that the inserted regulatory element is operably linked to the endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene. For example, an endogenous 9118, 990, 17662, 81982, 630, 21472, 17692, 19290, 21620, 21689, 28899, 53659, 64549, 9465, 23544, 7366, 27417, 57259, 21844, 943, 2061, 5891, 9137, 13908, 14310, 17600, 25584, 27824, 28469, 38947, 53003, 965, 56639, 9661, 16052, 1521, 6662, 13913, 12405 or 5014 gene, e.g., a gene which is "transcriptionally silent," e.g., not normally expressed, or expressed only at very low levels, may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed gene product in that cell. Techniques such as targeted homologous recombinations, can be used to insert the heterologous DNA as described in, e.g., Chappel, US 5,272,071; WO 91/06667, published on May 16, 1991.

III. Predictive Medicine:

[0166] The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and/or nucleic acid expression as well as 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077,

1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, in the context of a biological sample (*e.g.*, blood, serum, cells, *e.g.*, endothelial cells, or tissue, *e.g.*, vascular tissue, lymphoid tissue, peripheral blood cells) to thereby determine whether an individual is afflicted with a predisposition or is experiencing AIDS or an HIV-related disorder. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing AIDS or an HIV-related disorder. For example, mutations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene can be assayed for in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby phophylactically treat an individual prior to the onset of AIDS or an HIV-related disorder.

[0167] Another aspect of the invention pertains to monitoring the influence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulators (*e.g.*, anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ribozymes) on the expression or activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 in clinical trials.

[0168] These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

[0169] To determine whether a subject is afflicted with a disease, a biological sample may be obtained from a subject and the biological sample may be contacted with a compound or an agent capable of detecting a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid (*e.g.*, mRNA or genomic DNA) that encodes a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, in the biological sample. A preferred agent for

detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or genomic DNA. The nucleic acid probe can be, for example, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid set forth in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion thereof, such as an oligonucleotide of at least 15, 20, 25, 30, 25, 40, 45, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

[0170] A preferred agent for detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein in a sample is an antibody capable of binding to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')2) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

[0171] The term "biological sample" is intended to include tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells, and fluids present within a subject. That is, the detection method of the invention can be used to detect 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA,

protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein include introducing into a subject a labeled anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[0172] In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA, such that the presence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA or genomic DNA in the control sample with the presence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA or genomic DNA in the test sample.

B. Prognostic Assays

[0173] The present invention further pertains to methods for identifying subjects having or at risk of developing a disease associated with aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity.

[0174] As used herein, the term "aberrant" includes a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity which deviates from the wild type 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity. Aberrant expression or activity includes increased or decreased expression or activity, as well as expression or activity which does not follow the wild type developmental pattern of expression or the subcellular pattern of expression. For example, aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity is intended to include the cases in which a mutation in the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene causes the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene to be under-expressed or over-expressed and situations in which such mutations result in a non-functional 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a protein which does not function in a wild-type fashion, *e.g.*, a protein which does not interact with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate, or one which interacts with a non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate.

[0175] The assays described herein, such as the preceding diagnostic assays or the following assays, can be used to identify a subject having or at risk of developing a disease. A biological sample may be obtained from a subject and tested for the presence or absence of a genetic alteration. For example, such genetic alterations can be detected by

ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 2) an addition of one or more nucleotides to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 3) a substitution of one or more nucleotides of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 4) a chromosomal rearrangement of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 5) an alteration in the level of a messenger RNA transcript of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 6) aberrant modification of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, 8) a non-wild type level of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -protein, 9) allelic loss of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, and 10) inappropriate post-translational modification of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -protein.

[0176] As described herein, there are a large number of assays known in the art which can be used for detecting genetic alterations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene. For example, a genetic alteration in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161,

81982 or 46777 gene may be detected using a probe/primer in a polymerase chain reaction (PCR) (see, *e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, *e.g.*, Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method includes collecting a biological sample from a subject, isolating nucleic acid (*e.g.*, genomic DNA, mRNA or both) from the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene under conditions such that hybridization and amplification of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

[0177] Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

[0178] In an alternative embodiment, mutations in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene from a biological sample can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis

and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

[0179] In other embodiments, genetic mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be identified by hybridizing biological sample derived and control nucleic acids, *e.g.*, DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotide probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7:244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2:753-759). For example, genetic mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al.* (1996) *supra.* Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential, overlapping probes. This step allows for the identification of point mutations. This step is followed by a second hybridization array that allows for the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

[0180] In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in a biological sample and detect mutations by comparing the sequence of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 in the biological sample with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert (1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger (1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeve, C. W. (1995) *Biotechniques* 19:448-53),

including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

[0181] Other methods for detecting mutations in the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the wild-type 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digest the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397 and Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

[0182] In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735,

1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence, *e.g.*, a wild-type 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, for example, U.S. Patent No. 5,459,039.

[0183] In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766; see also Cotton (1993) *Mutat. Res.* 285:125-144 and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen *et al.* (1991) *Trends Genet* 7:5).

[0184] In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers *et al.* (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to ensure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

[0185] Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

[0186] Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

[0187] Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule) to effectively treat a disease.

C. Monitoring of Effects During Clinical Trials

[0188] The present invention further provides methods for determining the effectiveness of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748,

47161, 81982 or 46777 modulator (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator identified herein) in treating a disease. For example, the effectiveness of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator in increasing 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or in upregulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, can be monitored in clinical trials of subjects exhibiting decreased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or downregulated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Alternatively, the effectiveness of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator in decreasing 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or in downregulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, can be monitored in clinical trials of subjects exhibiting increased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression, protein levels, or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. In such clinical trials, the expression or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, and preferably, other genes that have been implicated in nociception can be used as a "read out" or marker of the phenotype of a particular cell.

[0189] For example, and not by way of limitation, genes, including 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 , that are modulated in cells by treatment with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents which modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity on subjects suffering from AIDS or an HIV-related disorder in, for example, a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 and other genes implicated in the HIV-related disorder. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods described herein, or by measuring the levels of activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. This response state may be determined before, and at various points during treatment of the individual with the agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0190] In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, or small molecule identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the

agent; (ii) detecting the level of expression of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the pre-administration sample with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an embodiment, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

IV. Methods of Treatment:

[0191] The present invention provides for both prophylactic and therapeutic methods of treating a subject, *e.g.*, a human, at risk of (or susceptible to) a disease. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of

pharmacogenomics. "Pharmacogenomics," as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers to the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype").

[0192] Thus, another aspect of the invention provides methods for tailoring an subject's prophylactic or therapeutic treatment with either the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecules of the present invention or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

A. Prophylactic Methods

[0193] In one aspect, the invention provides a method for preventing in a subject, a disease by administering to the subject an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Subjects at risk for AIDS or an HIV-related disorder, *e.g.,* can be identified by, for example, any or a combination of the diagnostic or prognostic assays described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity, such that a disease is prevented or, alternatively, delayed in its progression. Depending on the type of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 aberrancy, for example, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or

46777 agonist or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

B. Therapeutic Methods

[0194] Described herein are methods and compositions whereby AIDS or an HIV-related disorder may be ameliorated. Certain urological disorders are brought about, at least in part, by an excessive level of a gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of at least one symptom of AIDS or an HIV-related disorder. Techniques for the reduction of gene expression levels or the activity of a protein are discussed below.

[0195] Alternatively, certain other HIV-related disorders are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a protein's activity. As such, an increase in the level of gene expression and/or the activity of such proteins would bring about the amelioration of at least one symptom of AIDS or an HIV-related disorder.

[0196] In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a gene's expression, or the activity of the gene product, will reinforce the protective effect it exerts. Some urological disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of a least one symptom of AIDS or an HIV-related disorder. Techniques for increasing target gene expression levels or target gene product activity levels are discussed herein.

[0197] Accordingly, another aspect of the invention pertains to methods of modulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 or agent that modulates one or more of the activities of 9145, 1725, 311, 837,

58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity associated with the cell (*e.g.*, an endothelial cell, ovarian cell, T-cell or monocyte). An agent that modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777, ligand or substrate), a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonist or antagonist, a peptidomimetic of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activities. Examples of such stimulatory agents include active 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and a nucleic acid molecule encoding 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 that has been introduced into the cell. In another embodiment, the agent inhibits one or more 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activities. Examples of such inhibitory agents include antisense 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules, anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786,

10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies, and 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, upregulates or downregulates) 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity. In another embodiment, the method involves administering a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity.

[0198] Stimulation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally downregulated and/or in which increased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect. Likewise, inhibition of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally upregulated and/or in which decreased 9145, 1725, 311, 837, 58305, 156, 14175, 50352,

32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect.

(i) Methods for Inhibiting Target Gene Expression, Synthesis, or Activity

[0199] As discussed above, genes involved in viral disorders may cause such disorders via an increased level of gene activity. In some cases, such up-regulation may have a causative or exacerbating effect on the disease state. A variety of techniques may be used to inhibit the expression, synthesis, or activity of such genes and/or proteins.

[0200] For example, compounds such as those identified through assays described above, which exhibit inhibitory activity, may be used in accordance with the invention to ameliorate at least one symptom of AIDS or an HIV-related disorder. Such molecules may include, but are not limited to, small organic molecules, peptides, antibodies, and the like.

[0201] For example, compounds can be administered that compete with endogenous ligand for the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. The resulting reduction in the amount of ligand-bound 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein will modulate endothelial cell physiology. Compounds that can be particularly useful for this purpose include, for example, soluble proteins or peptides, such as peptides comprising one or more of the extracellular domains, or portions and/or analogs thereof, of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, including, for example, soluble fusion proteins such as Ig-tailed fusion proteins. (For a discussion of the production of Ig-tailed fusion proteins, see, for example, U.S. Pat. No. 5,116,964). Alternatively, compounds, such as ligand analogs or antibodies, that bind to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 receptor site, but do not activate the protein, (*e.g.*, receptor-ligand antagonists) can be effective in inhibiting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein activity.

[0202] Further, antisense and ribozyme molecules which inhibit expression of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397,

13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene may also be used in accordance with the invention to inhibit aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene activity. Still further, triple helix molecules may be utilized in inhibiting aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene activity.

[0203] The antisense nucleic acid molecules used in the methods of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

[0204] In yet another embodiment, an antisense nucleic acid molecule used in the methods of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids. Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise

a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

[0205] In still another embodiment, an antisense nucleic acid used in the methods of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA transcripts to thereby inhibit translation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. A ribozyme having specificity for a 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611-encoding nucleic acid can be designed based upon the nucleotide sequence of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 cDNA disclosed herein (*i.e.*, SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611-encoding mRNA (see, for example, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, for example, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418).

[0206] 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression can also be inhibited by targeting nucleotide sequences complementary to the regulatory region of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 (*e.g.*, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786,

10220, 17822, 33945, 43748, 47161, 81982 or 46777 promoter and/or enhancers) to form triple helical structures that prevent transcription of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene in target cells (see, for example, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15).

[0207] Antibodies that are both specific for the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and interfere with its activity may also be used to modulate or inhibit 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein function. Such antibodies may be generated using standard techniques described herein, against the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein itself or against peptides corresponding to portions of the protein. Such antibodies include but are not limited to polyclonal, monoclonal, Fab fragments, single chain antibodies, or chimeric antibodies.

[0208] In instances where the target gene protein is intracellular and whole antibodies are used, internalizing antibodies may be preferred. Lipofectin liposomes may be used to deliver the antibody or a fragment of the Fab region which binds to the target epitope into cells. Where fragments of the antibody are used, the smallest inhibitory fragment which binds to the target protein's binding domain is preferred. For example, peptides having an amino acid sequence corresponding to the domain of the variable region of the antibody that binds to the target gene protein may be used. Such peptides may be synthesized chemically or produced via recombinant DNA technology using methods well known in the art (described in, for example, Creighton (1983), *supra*; and Sambrook *et al.* (1989) *supra*). Single chain neutralizing antibodies which bind to intracellular target gene epitopes may also be administered. Such single chain antibodies may be administered, for example, by expressing nucleotide sequences encoding single-chain antibodies within the target cell population by utilizing, for example, techniques such as those described in Marasco *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:7889-7893).

[0209] In some instances, the target gene protein is extracellular, or is a transmembrane protein, such as the 9145, 1725, 311, 837, 58305, 156, 14175, 50352,

32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Antibodies that are specific for one or more extracellular domains of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, for example, and that interfere with its activity, are particularly useful in treating AIDS or an HIV-related disorder. Such antibodies are especially efficient because they can access the target domains directly from the bloodstream. Any of the administration techniques described below which are appropriate for peptide administration may be utilized to effectively administer inhibitory target gene antibodies to their site of action.

(ii) Methods for Restoring or Enhancing Target Gene Activity

[0210] Genes that cause AIDS or an HIV-related disorder may be underexpressed within BPH and/or UI. Alternatively, the activity of the protein products of such genes may be decreased, leading to the development of AIDS or an HIV-related disorder. Such down-regulation of gene expression or decrease of protein activity might have a causative or exacerbating effect on the disease state.

[0211] In some cases, genes that are up-regulated in the disease state might be exerting a protective effect. A variety of techniques may be used to increase the expression, synthesis, or activity of genes and/or proteins that exert a protective effect in response to AIDS or an HIV-related disorder.

[0212] Described in this section are methods whereby the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity may be increased to levels wherein the symptoms of the HIV-related disorder are ameliorated. The level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity may be increased, for example, by either increasing the level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene expression or by increasing the level of active 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein which is present.

[0213] For example, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, at a level sufficient to ameliorate at least one symptom of AIDS or an HIV-related disorder may be administered to a patient exhibiting such symptoms. Any of the techniques discussed below may be used for such administration. One of skill in the art will readily know how to determine the concentration of effective, non-toxic doses of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, utilizing techniques such as those described below.

[0214] Additionally, RNA sequences encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein may be directly administered to a patient exhibiting AIDS or an HIV-related disorder, at a concentration sufficient to produce a level of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein such that AIDS or an HIV-related disorder are ameliorated. Any of the techniques discussed below, which achieve intracellular administration of compounds, such as, for example, liposome administration, may be used for the administration of such RNA molecules. The RNA molecules may be produced, for example, by recombinant techniques such as those described herein.

[0215] Further, subjects may be treated by gene replacement therapy. One or more copies of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene, or a portion thereof, that directs the production of a normal 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 function, may be inserted into cells using vectors which include, but are not limited to adenovirus, adeno-associated virus, and retrovirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes. Additionally, techniques such as those described above may be used for the introduction of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077,

1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene sequences into human cells.

[0216] Cells, preferably, autologous cells, containing 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expressing gene sequences may then be introduced or reintroduced into the subject at positions which allow for the amelioration of at least one symptom of AIDS or an HIV-related disorder. Such cell replacement techniques may be preferred, for example, when the gene product is a secreted, extracellular gene product.

C. Pharmaceutical Compositions

[0217] Another aspect of the invention pertains to methods for treating a subject suffering from a disease. These methods involve administering to a subject an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity (*e.g.*, an agent identified by a screening assay described herein), or a combination of such agents. In another embodiment, the method involves administering to a subject a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 expression or activity.

[0218] Stimulation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally downregulated and/or in which increased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect. Likewise, inhibition of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is desirable in situations in which 9145, 1725, 311, 837,

58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 is abnormally upregulated and/or in which decreased 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity is likely to have a beneficial effect.

[0219] The agents which modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity can be administered to a subject using pharmaceutical compositions suitable for such administration. Such compositions typically comprise the agent (*e.g.*, nucleic acid molecule, protein, or antibody) and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0220] A pharmaceutical composition used in the therapeutic methods of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0221] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the

extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0222] Sterile injectable solutions can be prepared by incorporating the agent that modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity (*e.g.*, a fragment of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or an anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0223] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0224] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0225] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0226] The agents that modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0227] In one embodiment, the agents that modulate 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery

systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0228] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the agent that modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an agent for the treatment of subjects.

[0229] Toxicity and therapeutic efficacy of such agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD50/ED50. Agents which exhibit large therapeutic indices are preferred. While agents that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such agents to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0230] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulating agents lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon

the dosage form employed and the route of administration utilized. For any agent used in the therapeutic methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0231] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[0232] In a preferred example, a subject is treated with antibody, protein, or polypeptide in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody, protein, or polypeptide used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent from the results of diagnostic assays as described herein.

[0233] The present invention encompasses agents which modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e*,. including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams

per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

[0234] Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). It is

[0235] furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[0236] Further, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not

limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[0237] The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0238] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[0239] The nucleic acid molecules used in the methods of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be

delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by stereotactic injection (see, *e.g.*, Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

D. Pharmacogenomics

[0240] In conjunction with the therapeutic methods of the invention, pharmacogenomics (*i.e.*, the study of the relationship between a subject's genotype and that subject's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity, as well as tailoring the dosage and/or therapeutic regimen of treatment with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0241] Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp.Pharmacol. Physiol.* 23(10-11): 983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example,

glucose-6-phosphate aminopeptidase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

[0242] One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

[0243] Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug target is known (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein used in the methods of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

[0244] As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and the cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug

response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

[0245] Alternatively, a method termed the "gene expression profiling" can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (*e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecule or 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator used in the methods of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

[0246] Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of a subject. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and, thus, enhance therapeutic or prophylactic efficiency when treating a subject suffering from AIDS or an HIV-related disorder, with an agent which modulates 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

V. Recombinant Expression Vectors and Host Cells Used in the Methods of the Invention

[0247] The methods of the invention (*e.g.*, the screening assays described herein) include the use of vectors, preferably expression vectors, containing a nucleic acid

encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0248] The recombinant expression vectors to be used in the methods of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel (1990) *Methods Enzymol.* 185:3-7. Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cells and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be

appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, mutant forms of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, fusion proteins, and the like).

[0249] The recombinant expression vectors to be used in the methods of the invention can be designed for expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins in prokaryotic or eukaryotic cells. For example, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells, or mammalian cells. Suitable host cells are discussed further in Goeddel (1990) *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[0250] Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and

pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

[0251] Purified fusion proteins can be utilized in 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity assays, (*e.g.*, direct assays or competitive assays described in detail below), or to generate antibodies specific for 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins. In a preferred embodiment, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (*e.g.*, six weeks).

[0252] In another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J. *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

[0253] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid).

[0254] The methods of the invention may further use a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. Regulatory sequences operatively

linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific, or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes, see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

[0255] Another aspect of the invention pertains to the use of host cells into which a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule of the invention is introduced, *e.g.*, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule within a recombinant expression vector or a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecule containing sequences which allow it to homologously recombine into a specific site of the host cell's genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0256] A host cell can be any prokaryotic or eukaryotic cell. For example, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[0257] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms

"transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

[0258] A host cell used in the methods of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Accordingly, the invention further provides methods for producing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein has been introduced) in a suitable medium such that a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is produced. In another embodiment, the method further comprises isolating a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein from the medium or the host cell.

VI. Isolated Nucleic Acid Molecules Used in the Methods of the Invention

[0259] The methods of the invention include the use of isolated nucleic acid molecules that encode 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding nucleic acid

molecules (e.g., 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA) and fragments for use as PCR primers for the amplification or mutation of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

[0260] A nucleic acid molecule used in the methods of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, as a hybridization probe, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

[0261] Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51.

[0262] A nucleic acid used in the methods of the invention can be amplified using cDNA, mRNA or, alternatively, genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. Furthermore, oligonucleotides corresponding to 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

[0263] In a preferred embodiment, the isolated nucleic acid molecules used in the methods of the invention comprise the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, a complement of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 thereby forming a stable duplex.

[0264] In still another preferred embodiment, an isolated nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or a portion of any of this nucleotide sequence.

[0265] Moreover, the nucleic acid molecules used in the methods of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, *e.g.*, a biologically active portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, of an anti-sense sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, or of a naturally occurring allelic variant or mutant of SEQ ID

NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51. In one embodiment, a nucleic acid molecule used in the methods of the present invention comprises a nucleotide sequence which is greater than 100, 100-200, 200-300, 300-400, 400-500, 500-600, 600-700, 700-800, 800-900, 900-1000, 1000-1100, 1100-1200, 1200-1300, or more nucleotides in length and hybridizes under stringent hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51.

[0266] As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences that are significantly identical or homologous to each other remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, Ausubel *et al.*, eds., John Wiley & Sons, Inc. (1995), sections 2, 4 and 6. Additional stringent conditions can be found in *Molecular Cloning: A Laboratory Manual*, Sambrook *et al.*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), chapters 7, 9 and 11. A preferred, non-limiting example of stringent hybridization conditions includes hybridization in 4X sodium chloride/sodium citrate (SSC), at about 65-70°C (or hybridization in 4X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 1X SSC, at about 65-70°C. A preferred, non-limiting example of highly stringent hybridization conditions includes hybridization in 1X SSC, at about 65-70°C (or hybridization in 1X SSC plus 50% formamide at about 42-50°C) followed by one or more washes in 0.3X SSC, at about 65-70°C. A preferred, non-limiting example of reduced stringency hybridization conditions includes hybridization in 4X SSC, at about 50-60°C (or alternatively hybridization in 6X SSC plus 50% formamide at about 40-45°C) followed by one or more washes in 2X SSC, at about 50-60°C. Ranges intermediate to the above-recited values, *e.g.*, at 65-70°C or at 42-50°C are also intended to be encompassed by the present invention. SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes each after hybridization is complete. The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the

hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(°C) = 2(\#\text{ of A + T bases}) + 4(\#\text{ of G + C bases})$. For hybrids between 18 and 49 base pairs in length, $T_m(°C) = 81.5 + 16.6(\log_{10}[Na^+]) + 0.41(\%G+C) - (600/N)$, where N is the number of bases in the hybrid, and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1xSSC = 0.165 M). It will also be recognized by the skilled practitioner that additional reagents may be added to hybridization and/or wash buffers to decrease non-specific hybridization of nucleic acid molecules to membranes, for example, nitrocellulose or nylon membranes, including but not limited to blocking agents (*e.g.*, BSA or salmon or herring sperm carrier DNA), detergents (*e.g.*, SDS), chelating agents (*e.g.*, EDTA), Ficoll, PVP and the like. When using nylon membranes, in particular, an additional preferred, non-limiting example of stringent hybridization conditions is hybridization in 0.25-0.5M NaH_2PO_4, 7% SDS at about 65°C, followed by one or more washes at 0.02M NaH_2PO_4, 1% SDS at 65°C, see *e.g.*, Church and Gilbert (1984) *Proc. Natl. Acad. Sci. USA* 81:1991-1995, (or alternatively 0.2X SSC, 1% SDS).

[0267] In preferred embodiments, the probe further comprises a label group attached thereto, *e.g.*, the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissue which misexpress a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, such as by measuring a level of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA levels or determining whether a genomic 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene has been mutated or deleted.

[0268] The methods of the invention further encompass the use of nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, due to degeneracy of the genetic code and thus encode the same 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735,

1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51. In another embodiment, an isolated nucleic acid molecule included in the methods of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52.

[0269] The methods of the invention further include the use of allelic variants of human 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611, *e.g.*, functional and non-functional allelic variants. Functional allelic variants are naturally occurring amino acid sequence variants of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein that maintain a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52 or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

[0270] Non-functional allelic variants are naturally occurring amino acid sequence variants of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein that do not have a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Non-functional allelic variants will typically contain a non-conservative substitution, deletion, or insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, or a substitution, insertion or deletion in critical residues or critical regions of the protein.

[0271] The methods of the present invention may further use non-human orthologues of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Orthologues of the human 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein are proteins that are

isolated from non-human organisms and possess the same 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0272] The methods of the present invention further include the use of nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51 or a portion thereof, in which a mutation has been introduced. The mutation may lead to amino acid substitutions at "non-essential" amino acid residues or at "essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 (*e.g.*, the sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins of the present invention are not likely to be amenable to alteration.

[0273] Mutations can be introduced into SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is preferably replaced with another amino

acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using the assay described herein.

[0274] Another aspect of the invention pertains to the use of isolated nucleic acid molecules which are antisense to the nucleotide sequence of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 or 51. An "antisense" nucleic acid comprises a nucleotide sequence which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 coding strand, or to only a portion thereof. In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (also referred to as 5' and 3' untranslated regions).

[0275] Given the coding strand sequences encoding 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735,

1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic

acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest). Antisense nucleic acid molecules used in the methods of the invention are further described above, in section IV.

[0276] In yet another embodiment, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules used in the methods of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci.* 93:14670-675.

[0277] PNAs of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can be used in the therapeutic and diagnostic applications described herein. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (*e.g.*, by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (*e.g.*, S1 nucleases (Hyrup B. *et al.* (1996) *supra*)); or as probes or primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* (1996) *supra*).

[0278] In another embodiment, PNAs of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220,

17822, 33945, 43748, 47161, 81982 or 46777 can be modified, (*e.g.*, to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (*e.g.*, RNAse H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. *et al.* (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. *et al.* (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et al.* (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. *et al.* (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. *et al.* (1975) *Bioorganic Med. Chem. Lett.* 5: 1119-11124).

[0279] In other embodiments, the oligonucleotide used in the methods of the invention may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, *e.g.*, Krol *et al.* (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, *e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

VII. Isolated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 Proteins and Anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 Antibodies Used in the Methods of the Invention

[0280] The methods of the invention include the use of isolated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies. In one embodiment, native 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

[0281] As used herein, a "biologically active portion" of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein includes a fragment of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein having a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity. Biologically active portions of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein include peptides comprising amino acid sequences sufficiently identical to or derived from the

amino acid sequence of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, which include fewer amino acids than the full length 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins, and exhibit at least one activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (*e.g.*, the N-terminal region of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein that is believed to be involved in the regulation of apoptotic activity). A biologically active portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be a polypeptide which is, for example, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300 or more amino acids in length. Biologically active portions of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be used as targets for developing agents which modulate a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 activity.

[0282] In a preferred embodiment, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein used in the methods of the invention has an amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52. In other embodiments, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein is substantially identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26,

28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, and retains the functional activity of the protein of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection V above. Accordingly, in another embodiment, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein used in the methods of the invention is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical to SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52.

[0283] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 amino acid sequence of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 or 52, having 500 amino acid residues, at least 75, preferably at least 150, more preferably at least 225, even more preferably at least 300, and even more preferably at least 400 or more amino acid residues are aligned). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[0284] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred

embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.* 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[0285] The methods of the invention may also use 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 chimeric or fusion proteins. As used herein, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 "chimeric protein" or "fusion protein" comprises a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide operatively linked to a non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide. An "9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecule, whereas a "non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, *e.g.*, a protein which is

different from the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein and which is derived from the same or a different organism. Within a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide can correspond to all or a portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. In a preferred embodiment, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein comprises at least one biologically active portion of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. In another preferred embodiment, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein comprises at least two biologically active portions of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide and the non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide are fused in-frame to each other. The non-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide can be fused to the N-terminus or C-terminus of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide.

[0286] For example, in one embodiment, the fusion protein is a GST-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644,

19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion protein in which the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant 34021, 1720, 1683, 1552, 1682, 1675, 12825, 9952, 5816, 10002 or 1611.

[0287] In another embodiment, this fusion protein is a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be increased through use of a heterologous signal sequence.

[0288] The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins used in the methods of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins can be used to affect the bioavailability of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate. Use of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fusion proteins may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein; (ii) mis-regulation of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 gene; and (iii) aberrant post-translational modification of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397,

13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0289] Moreover, the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -fusion proteins used in the methods of the invention can be used as immunogens to produce anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies in a subject, to purify 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 ligands and in screening assays to identify molecules which inhibit the interaction of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 substrate.

[0290] Preferably, a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 chimeric or fusion protein used in the methods of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -encoding

nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0291] The present invention also pertains to the use of variants of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins which function as either 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonists (mimetics) or as 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antagonists. Variants of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. An agonist of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. An antagonist of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can inhibit one or more of the activities of the naturally occurring form of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein by, for example, competitively modulating a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 -mediated activity of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Thus, specific biological effects can be elicited by treatment with a variant of limited

function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0292] In one embodiment, variants of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein which function as either 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 agonists (mimetics) or as 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein for 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein agonist or antagonist activity. In one embodiment, a variegated library of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences therein. There are a variety of methods which can be used to produce libraries of potential 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397,

13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477).

[0293] In addition, libraries of fragments of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein coding sequence can be used to generate a variegated population of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 fragments for screening and subsequent selection of variants of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein.

[0294] Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA

libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 proteins. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

[0295] The methods of the present invention further include the use of anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies. An isolated 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 using standard techniques for polyclonal and monoclonal antibody preparation. A full-length 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein can be used or, alternatively, antigenic peptide fragments of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be used as immunogens. The antigenic peptide of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 comprises at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48,

50 or 52, and encompasses an epitope of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 such that an antibody raised against the peptide forms a specific immune complex with the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.

[0296] Preferred epitopes encompassed by the antigenic peptide are regions of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

[0297] A 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 immunogen is typically used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse, or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein or a chemically synthesized 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 preparation induces a polyclonal anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody response.

[0298] The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen,

such as a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 molecules. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . A monoclonal antibody composition thus typically displays a single binding affinity for a particular 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein with which it immunoreacts.

[0299] Polyclonal anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies can be prepared as described above by immunizing a suitable subject with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 immunogen. The anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . If desired, the antibody molecules directed against 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the anti-

9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally Kenneth, R. H. in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); Lerner, E. A. (1981) *Yale J. Biol. Med.* 54:387-402; Gefter, M. L. *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 .

[0300] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* (1977) *supra*; Lerner (1981) *supra*; and Kenneth (1980) *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium

containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 , *e.g.*, using a standard ELISA assay.

[0301] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 to thereby isolate immunoglobulin library members that bind 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 . Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse

et al. (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* (1990) *Nature* 348:552-554.

[0302] Additionally, recombinant anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the methods of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

[0303] An anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody can be used to detect 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 protein. Anti-9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865,

12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[0304] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figure and the Sequence Listing is incorporated herein by reference.

EXAMPLES

EXAMPLE 1: TISSUE DISTRIBUTION OF USING TAQMAN™ ANALYSIS

[0305] This example describes the TaqMan™ procedure. The Taqman™ procedure is a quantitative, reverse transcription PCR-based approach for detecting mRNA. The RT-PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold™ DNA Polymerase to cleave a TaqMan™ probe during PCR. Briefly, cDNA was generated from the samples of interest, *e.g.*, heart, kidney, liver, skeletal muscle, and various vessels, and used as the starting material for PCR amplification. In addition to the 5' and 3' gene-specific primers, a gene-specific oligonucleotide probe (complementary to the region being amplified) was included in the reaction (*i.e.*, the Taqman™ probe). The TaqMan™ probe includes the oligonucleotide with a fluorescent reporter dye covalently linked to the 5' end

of the probe (such as FAM (6-carboxyfluorescein), TET (6-carboxy-4,7,2',7'-tetrachlorofluorescein), JOE (6-carboxy-4,5-dichloro-2,7-dimethoxyfluorescein), or VIC) and a quencher dye (TAMRA (6-carboxy-N,N,N',N'-tetramethylrhodamine) at the 3' end of the probe.

[0306] During the PCR reaction, cleavage of the probe separates the reporter dye and the quencher dye, resulting in increased fluorescence of the reporter. Accumulation of PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye. When the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of interest is present, the probe specifically anneals between the forward and reverse primer sites. The 5'-3' nucleolytic activity of the AmpliTaq™ Gold DNA Polymerase cleaves the probe between the reporter and the quencher only if the probe hybridizes to the target. The probe fragments are then displaced from the target, and polymerization of the strand continues. The 3' end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. RNA was prepared using the trizol method and treated with DNase to remove contaminating genomic DNA. cDNA was synthesized using standard techniques. Mock cDNA synthesis in the absence of reverse transcriptase resulted in samples with no detectable PCR amplification of the control gene confirms efficient removal of genomic DNA contamination.

Equivalents

[0307] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed:

1. A method for identifying a compound capable of treating AIDS or an HIV-related disorder, comprising:

a) combining a compound to be tested with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide under conditions suitable for binding of the test compound to the polypeptide; and

b) detecting binding of the test compound to the polypeptide to thereby identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating AIDS or an HIV-related disorder.

2. The method of claim 1, wherein the compound is selected from the group consisting of a small molecule, a peptide or an antibody.

3. The method of claim 1, wherein the polypeptide further comprises heterologous sequences.

4. The method of claim 1, wherein the polypeptide is an isolated polypeptide, a membrane-bound form of an isolated polypeptide or a cell comprising the polypeptide.

5. The method of claim 4, wherein the cell is an AIDS- or HIV-related cell.

6. The method of claim 1, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

a) a competition binding assay;

b) an immunoassay; and

c) a yeast two-hybrid assay.

7. A method for identifying a compound capable of treating AIDS or an HIV-related disorder, comprising:

a) combining a compound to be tested with a host cell expressing a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777

polypeptide under conditions suitable for binding of the test compound to the polypeptide; and

b) detecting binding of the test compound to the polypeptide to thereby identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating AIDS or an HIV-related disorder.

8. The method of claim 7, wherein the compound is selected from the group consisting of a small molecule, a peptide, an antibody or an antisense nucleic acid molecule.

9. The method of claim 7, wherein the polypeptide further comprises heterologous sequences.

10. The method of claim 7, wherein the host cell is an AIDS- or HIV-related cell.

11. The method of claim 7, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

a) a competition binding assay;

b) an immunoassay; and

c) a yeast two-hybrid assay.

12. A method of identifying a subject having AIDS or an HIV-related disorder, or at risk for developing AIDS or an HIV-related disorder comprising:

a) contacting a sample obtained from the subject comprising polypeptides with a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding substance; and

b) detecting the presence of a polypeptide in the sample that binds to the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 binding substance, thereby identifying a subject having AIDS or an HIV-related disorder, or at risk for developing AIDS or an HIV-related disorder.

13. The method of claim 12, wherein the binding substance is an antibody.

14. The method of claim 12, wherein the binding substance is detectably labeled.

15. A method for treating a subject having AIDS or an HIV-related disorder characterized by aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide activity or aberrant 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid expression comprising administering to the subject a 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator, thereby treating said subject having AIDS or an HIV-related disorder.

16. The method of claim 15, wherein the disorder is a disorder associated with but not limited to AIDS or an HIV-related disorder.

17. The method of claim 15, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is administered in a pharmaceutically acceptable formulation.

18. The method of claim 15, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is capable of modulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 polypeptide activity.

19. The method of claim 18, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is an anti-9145, 1725,

311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 antibody.

20. The method of claim 15, wherein the 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 modulator is capable of modulating 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982 or 46777 nucleic acid expression.

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cac ctg cac agt ctc aac ctg ctg agc agt gag ggt ggc agc gac gag   1444
His Leu His Ser Leu Asn Leu Leu Ser Ser Glu Gly Gly Ser Asp Glu
            460                 465                 470

cat gac atc aac ttt ctg atg aag atg gcc ctt gac aag atc gcc ttt   1492
His Asp Ile Asn Phe Leu Met Lys Met Ala Leu Asp Lys Ile Ala Phe
        475                 480                 485

atc ccc ttc agc tac ctc gtc gat cag tgg cgc tgg agg gta ttt gat   1540
Ile Pro Phe Ser Tyr Leu Val Asp Gln Trp Arg Trp Arg Val Phe Asp
    490                 495                 500

gga agc atc acc aag gag aac tat aac cag gag tgg tgg agc ctc agg   1588
Gly Ser Ile Thr Lys Glu Asn Tyr Asn Gln Glu Trp Trp Ser Leu Arg
505                 510                 515                 520

ctg aag tac cag ggc ctc tgc ccc cca gtg ccc agg act caa ggt gac   1636
Leu Lys Tyr Gln Gly Leu Cys Pro Pro Val Pro Arg Thr Gln Gly Asp
                525                 530                 535

ttt gac cca ggg gcc aag ttc cac att cct tct agc gtg cct tac atc   1684
Phe Asp Pro Gly Ala Lys Phe His Ile Pro Ser Ser Val Pro Tyr Ile
            540                 545                 550

agg tac ttt gtc agc ttc atc atc cag ttc cag ttc cac gag gca ctg   1732
Arg Tyr Phe Val Ser Phe Ile Ile Gln Phe Gln Phe His Glu Ala Leu
        555                 560                 565

tgc cag gca gct ggc cac acg ggc ccc ctg cac aag tgt gac atc tac   1780
Cys Gln Ala Ala Gly His Thr Gly Pro Leu His Lys Cys Asp Ile Tyr
    570                 575.                580

cag tcc aag gag gcc ggg cag cgc ctg gcg acc gcc atg aag ctg ggc   1828
Gln Ser Lys Glu Ala Gly Gln Arg Leu Ala Thr Ala Met Lys Leu Gly
585                 590                 595                 600

ttc agt agg ccg tgg ccg gaa gcc atg cag ctg atc acg ggc cag ccc   1876
Phe Ser Arg Pro Trp Pro Glu Ala Met Gln Leu Ile Thr Gly Gln Pro
                605                 610                 615

aac atg agc gcc tcg gcc atg ttg agc tac ttc aag ccg ctg ctg gac   1924
Asn Met Ser Ala Ser Ala Met Leu Ser Tyr Phe Lys Pro Leu Leu Asp
            620                 625                 630

tgg ctc cgc acg gag aac gag ctg cat ggg gag aag ctg ggc tgg ccg   1972
Trp Leu Arg Thr Glu Asn Glu Leu His Gly Glu Lys Leu Gly Trp Pro
        635                 640                 645

cag tac aac tgg acg ccg aac tcc gct cgc tca gaa ggg ccc ctc cca   2020
Gln Tyr Asn Trp Thr Pro Asn Ser Ala Arg Ser Glu Gly Pro Leu Pro
    650                 655                 660

gac agc ggc cgc gtc agc ttc ctg ggc ctg gac ctg gat gcg cag cag   2068
Asp Ser Gly Arg Val Ser Phe Leu Gly Leu Asp Leu Asp Ala Gln Gln
665                 670                 675                 680

gcc cgc gtg ggc cag tgg ctg ctg ctc ttc ctg ggc atc gcc ctg ctg   2116
Ala Arg Val Gly Gln Trp Leu Leu Leu Phe Leu Gly Ile Ala Leu Leu
                685                 690                 695
```

```
gta gcc acc ctg ggc ctc agc cag cgg ctc ttc agc atc cgc cac cgc   2164
Val Ala Thr Leu Gly Leu Ser Gln Arg Leu Phe Ser Ile Arg His Arg
            700                 705                 710

agc ctc cac cgg cac tcc cac ggg ccc cag ttc ggc tcc gag gtg gag   2212
Ser Leu His Arg His Ser His Gly Pro Gln Phe Gly Ser Glu Val Glu
        715                 720                 725

ctg aga cac tcc tga ggtgacccgg ctgggtcggc cctgcccaag ggcctcccac   2267
Leu Arg His Ser  *
    730

cagagactgg gatgggaaca ctggtgggca gctgaggaca caccccacac cccagcccac 2327
cctgctcctc ctgccctgtc cctgtccccc tcccctccca gtcctccacc accagccgcc 2387
ccagcccctt ctcccagcac acggctgcct gacactgagc cccacctctc caagtctccc 2447
tgtgaataca attaaaggtc ctgccctccc a                                2478

<210> 4
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<212> PRT
<213> Homo sapiens

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Met Gly Gln Gly Trp Ala Thr Ala Gly Leu Pro Ser Leu Leu Phe Leu
 1               5                  10                  15
Leu Leu Cys Tyr Gly His Pro Leu Leu Val Pro Ser Gln Glu Ala Ser
            20                  25                  30
Gln Gln Val Thr Val Thr His Gly Thr Ser Ser Gln Ala Thr Thr Ser
        35                  40                  45
Ser Gln Thr Thr Thr His Gln Ala Thr Ala His Gln Thr Ser Ala Gln
    50                  55                  60
Ser Pro Asn Leu Val Thr Asp Glu Ala Glu Ala Ser Lys Phe Val Glu
65                  70                  75                  80
Glu Tyr Asp Arg Thr Ser Gln Val Val Trp Asn Glu Tyr Ala Glu Ala
                85                  90                  95
Asn Trp Asn Tyr Asn Thr Asn Ile Thr Thr Glu Thr Ser Lys Ile Leu
            100                 105                 110
Leu Gln Lys Asn Met Gln Ile Ala Asn His Thr Leu Lys Tyr Gly Thr
        115                 120                 125
Gln Ala Arg Lys Phe Asp Val Asn Gln Leu Gln Asn Thr Thr Ile Lys
    130                 135                 140
Arg Ile Ile Lys Lys Val Gln Asp Leu Glu Arg Ala Ala Leu Pro Ala
145                 150                 155                 160
Gln Glu Leu Glu Glu Tyr Asn Lys Ile Leu Leu Asp Met Glu Thr Thr
                165                 170                 175
Tyr Ser Val Ala Thr Val Cys His Pro Asn Gly Ser Cys Leu Gln Leu
            180                 185                 190
Glu Pro Asp Leu Thr Asn Val Met Ala Thr Ser Arg Lys Tyr Glu Asp
        195                 200                 205
Leu Leu Trp Ala Trp Glu Gly Trp Arg Asp Lys Ala Gly Arg Ala Ile
    210                 215                 220
Leu Gln Phe Tyr Pro Lys Tyr Val Glu Leu Ile Asn Gln Ala Ala Arg
225                 230                 235                 240
Leu Asn Gly Tyr Val Asp Ala Gly Asp Ser Trp Arg Ser Met Tyr Glu
                245                 250                 255
Thr Pro Ser Leu Glu Gln Asp Leu Glu Arg Leu Phe Gln Glu Leu Gln
            260                 265                 270
Pro Leu Tyr Leu Asn Leu His Ala Tyr Val Arg Arg Ala Leu His Arg
        275                 280                 285
His Tyr Gly Ala Gln His Ile Asn Leu Glu Gly Pro Ile Pro Ala His
    290                 295                 300
```

```
Leu Leu Gly Asn Met Trp Ala Gln Thr Trp Ser Asn Ile Tyr Asp Leu
305                 310                 315                 320
Val Val Pro Phe Pro Ser Ala Pro Ser Met Asp Thr Thr Glu Ala Met
                325                 330                 335
Leu Lys Gln Gly Trp Thr Pro Arg Arg Met Phe Lys Glu Ala Asp Asp
            340                 345                 350
Phe Phe Thr Ser Leu Gly Leu Leu Pro Val Pro Pro Glu Phe Trp Asn
        355                 360                 365
Lys Ser Met Leu Glu Lys Pro Thr Asp Gly Arg Glu Val Val Cys His
    370                 375                 380
Ala Ser Ala Trp Asp Phe Tyr Asn Gly Lys Asp Phe Arg Ile Lys Gln
385                 390                 395                 400
Cys Thr Thr Val Asn Leu Glu Asp Leu Val Val Ala His His Glu Met
                405                 410                 415
Gly His Ile Gln Tyr Phe Met Gln Tyr Lys Asp Leu Pro Val Ala Leu
            420                 425                 430
Arg Glu Gly Ala Asn Pro Gly Phe His Glu Ala Ile Gly Asp Val Leu
        435                 440                 445
Ala Leu Ser Val Ser Thr Pro Lys His Leu His Ser Leu Asn Leu Leu
    450                 455                 460
Ser Ser Glu Gly Gly Ser Asp Glu His Asp Ile Asn Phe Leu Met Lys
465                 470                 475                 480
Met Ala Leu Asp Lys Ile Ala Phe Ile Pro Phe Ser Tyr Leu Val Asp
                485                 490                 495
Gln Trp Arg Trp Arg Val Phe Asp Gly Ser Ile Thr Lys Glu Asn Tyr
            500                 505                 510
Asn Gln Glu Trp Trp Ser Leu Arg Leu Lys Tyr Gln Gly Leu Cys Pro
        515                 520                 525
Pro Val Pro Arg Thr Gln Gly Asp Phe Asp Pro Gly Ala Lys Phe His
    530                 535                 540
Ile Pro Ser Ser Val Pro Tyr Ile Arg Tyr Phe Val Ser Phe Ile Ile
545                 550                 555                 560
Gln Phe Gln Phe His Glu Ala Leu Cys Gln Ala Ala Gly His Thr Gly
                565                 570                 575
Pro Leu His Lys Cys Asp Ile Tyr Gln Ser Lys Glu Ala Gly Gln Arg
            580                 585                 590
Leu Ala Thr Ala Met Lys Leu Gly Phe Ser Arg Pro Trp Pro Glu Ala
        595                 600                 605
Met Gln Leu Ile Thr Gly Gln Pro Asn Met Ser Ala Ser Ala Met Leu
    610                 615                 620
Ser Tyr Phe Lys Pro Leu Leu Asp Trp Leu Arg Thr Glu Asn Glu Leu
625                 630                 635                 640
His Gly Glu Lys Leu Gly Trp Pro Gln Tyr Asn Trp Thr Pro Asn Ser
                645                 650                 655
Ala Arg Ser Glu Gly Pro Leu Pro Asp Ser Gly Arg Val Ser Phe Leu
            660                 665                 670
Gly Leu Asp Leu Asp Ala Gln Gln Ala Arg Val Gly Gln Trp Leu Leu
        675                 680                 685
Leu Phe Leu Gly Ile Ala Leu Leu Val Ala Thr Leu Gly Leu Ser Gln
    690                 695                 700
Arg Leu Phe Ser Ile Arg His Arg Ser Leu His Arg His Ser His Gly
705                 710                 715                 720
Pro Gln Phe Gly Ser Glu Val Glu Leu Arg His Ser
                725                 730
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<213> Homo sapiens

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atg aat cgg cac cat ctg cag gat cac ttt ctg gaa ata gac aag aag 108
Met Asn Arg His His Leu Gln Asp His Phe Leu Glu Ile Asp Lys Lys
1 5 10 15

aac tgc tgt gtg ttc cga gat gac ttc att gcc aag gtg ttg ccg ccg 156
Asn Cys Cys Val Phe Arg Asp Asp Phe Ile Ala Lys Val Leu Pro Pro
20 25 30

gtg ttg ggg ctg gag ttt atc ttt ggg ctt ctg ggc aat ggc ctt gcc 204
Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala
35 40 45

ctg tgg att ttc tgt ttc cac ctc aag tcc tgg aaa tcc agc cgg att 252
Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile
50 55 60

ttc ctg ttc aac ctg gca gta gct gac ttt cta ctg atc atc tgc ctg 300
Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu
65 70 75 80

ccg ttc gtg atg gac tac tat gtg cgg cgt tca gac tgg aac ttt ggg 348
Pro Phe Val Met Asp Tyr Tyr Val Arg Arg Ser Asp Trp Asn Phe Gly
85 90 95

gac atc cct tgc cgg ctg gtg ctc ttc atg ttt gcc atg aac cgc cag 396
Asp Ile Pro Cys Arg Leu Val Leu Phe Met Phe Ala Met Asn Arg Gln
100 105 110

ggc agc atc atc ttc ctc acg gtg gtg gcg gta gac agg tat ttc cgg 444
Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg
115 120 125

gtg gtc cat ccc cac cac gcc ctg aac aag atc tcc aat tgg aca gca 492
Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Trp Thr Ala
130 135 140

gcc atc atc tct tgc ctt ctg tgg ggc atc act gtt ggc cta aca gtc 540
Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Val Gly Leu Thr Val
145 150 155 160

cac ctc ctg aag aag aag ttg ctg atc cag aat ggc cct gca aat gtg 588
His Leu Leu Lys Lys Lys Leu Leu Ile Gln Asn Gly Pro Ala Asn Val
165 170 175

tgc atc agc ttc agc atc tgc cat acc ttc cgg tgg cac gaa gct atg 636
Cys Ile Ser Phe Ser Ile Cys His Thr Phe Arg Trp His Glu Ala Met
180 185 190

ttc ctc ctg gag ttc ctc ctg ccc ctg ggc atc atc ctg ttc tgc tca 684
Phe Leu Leu Glu Phe Leu Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser
195 200 205

gcc aga att atc tgg agc ctg cgg cag aga caa atg gac cgg cat gcc 732
Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala
210 215 220

```
aag atc aag aga gcc atc acc ttc atc atg gtg gtg gcc atc gtc ttt   780
Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe
225                 230                 235                 240

gtc atc tgc ttc ctt ccc agc gtg gtt gtg cgg atc cgc atc ttc tgg   828
Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp
            245                 250                 255

ctc ctg cac act tcg ggc acg cag aat tgt gaa gtg tac cgc tcg gtg   876
Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val
        260                 265                 270

gac ctg gcg ttc ttt atc act ctc agc ttc acc tac atg aac agc atg   924
Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
    275                 280                 285

ctg gac ccc gtg gtg tac tac ttc tcc agc cca tcc ttt ccc aac ttc   972
Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe
290                 295                 300

ttc tcc act ttg atc aac cgc tgc ctc cag agg aag atg aca ggt gag   1020
Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu
305                 310                 315                 320

cca gat aat aac cgc agc acg agc gtc gag ctc aca ggg gac ccc aac   1068
Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn
                325                 330                 335

aaa acc aga ggc gct cca gag gcg tta atg gcc aac tcc ggt gag cca   1116
Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro
            340                 345                 350

tgg agc ccc tct tat ctg ggc cca acc tca aat aac cat tcc aag aag   1164
Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Asn Asn His Ser Lys Lys
        355                 360                 365

gga cat tgt cac caa gaa cca gca tct ctg gag aaa cag ttg ggc tgt   1212
Gly His Cys His Gln Glu Pro Ala Ser Leu Glu Lys Gln Leu Gly Cys
    370                 375                 380


tgc atc gag taa tgtcactgga ctcggcctaa ggtttcctgg aacttccaga       1264
Cys Ile Glu  *
385

ttcagagaat ctgatttagg gaaactgtgg cagatgagtg ggagactggt tgcaaggtgt 1324
gaccacagga atcctggagg aacagagagt aaagcttcta ggcatctgaa acttgcttca 1384
tctctgacgc tcgcaggact gaagatgggc aaattgtagg cgtttctgct gagcagagtt 1444
ggagccagag atctacttgt gacttgttgg ccttcttccc acatctgcct cagactgggg 1504
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gattagcccc agaagggact gagctaaaca gtgttattat gggaaaggaa atggcattgc 1804
tgctttcaac cagcgactaa tgcaatccat tcctctcttg tttatagtaa tctaagggtt 1864
gagcagttaa aacggcttca ggatagaaag ctgtttccca cctgtttcgt tttaccatta 1924
aaagggaaac gtgcctctgc cccacgggta gaggggtgc acgttcctcc tggttccttc 1984
gcttgtgttt ctgtacttac caaaaatcta ccacttcaat aaattttgat aggagacaaa 2044
aaaaaaa                                                           2051
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<213> Homo sapiens

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Met Asn Arg His His Leu Gln Asp His Phe Leu Glu Ile Asp Lys Lys
1 5 10 15
Asn Cys Cys Val Phe Arg Asp Asp Phe Ile Ala Lys Val Leu Pro Pro
20 25 30
Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala
35 40 45
Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile
50 55 60
Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu
65 70 75 80
Pro Phe Val Met Asp Tyr Tyr Val Arg Arg Ser Asp Trp Asn Phe Gly
85 90 95
Asp Ile Pro Cys Arg Leu Val Leu Phe Met Phe Ala Met Asn Arg Gln
100 105 110
Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg
115 120 125
Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Trp Thr Ala
130 135 140
Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Val Gly Leu Thr Val
145 150 155 160
His Leu Leu Lys Lys Lys Leu Leu Ile Gln Asn Gly Pro Ala Asn Val
165 170 175
Cys Ile Ser Phe Ser Ile Cys His Thr Phe Arg Trp His Glu Ala Met
180 185 190
Phe Leu Leu Glu Phe Leu Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser
195 200 205
Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala
210 215 220
Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe
225 230 235 240
Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp
245 250 255
Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val
260 265 270
Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
275 280 285
Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe
290 295 300
Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu
305 310 315 320
Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn
325 330 335
Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro
340 345 350
Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Asn Asn His Ser Lys Lys
355 360 365
Gly His Cys His Gln Glu Pro Ala Ser Leu Glu Lys Gln Leu Gly Cys
370 375 380
Cys Ile Glu
385

<210> 7

<211> 2087

<212> DNA
<213> Homo sapiens

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<222> (104)...(1612)

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gagacgtgga gcgcgccggc tcgctgcagc tccgggactc aac atg cgc tgc tcg 115
Met Arg Cys Ser
1

ccg gga ggc gtc tgg ctg ggc ctg gcc gcg tcg ctc ctg cac gtg tcc 163
Pro Gly Gly Val Trp Leu Gly Leu Ala Ala Ser Leu Leu His Val Ser
5 10 15 20

ctg caa ggc gag ttc cag agg aag ctt tac aag gag ctg gtc aag aac 211
Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu Leu Val Lys Asn
25 30 35

tac aat ccc ttg gag agg ccc gtg gcc aat gac tcg caa cca ctc acc 259
Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser Gln Pro Leu Thr
40 45 50

gtc tac ttc tcc ctg agc ctc ctg cag atc atg gac gtg gat gag aag 307
Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp Val Asp Glu Lys
55 60 65

aac caa gtt tta acc acc aac att tgg ctg caa atg tct tgg aca gat 355
Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met Ser Trp Thr Asp
70 75 80

cac tat tta cag tgg aat gtg tca gaa tat cca ggg gtg aag act gtt 403
His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly Val Lys Thr Val
85 90 95 100

cgt ttc cca gat ggc cag att tgg aaa cca gac att ctt ctc tat aac 451
Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile Leu Leu Tyr Asn
105 110 115

agt gct gat gag cgc ttt gac gcc aca ttc cac act aac gtg ttg gtg 499
Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr Asn Val Leu Val
120 125 130

aat tct tct ggg cat tgc cag tac ctg cct cca ggc ata ttc aag agt 547
Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly Ile Phe Lys Ser
135 140 145

tcc tgc tac atc gat gta cgc tgg ttt ccc ttt gat gtg cag cac tgc 595
Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp Val Gln His Cys
150 155 160

aaa ctg aag ttt ggg tcc tgg tct tac gga ggc tgg tcc ttg gat ctg 643
Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp Ser Leu Asp Leu
165 170 175 180

cag atg cag gag gca gat atc agt ggc tat atc ccc aat gga gaa tgg 691
Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro Asn Gly Glu Trp
185 190 195

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gac cta gtg gga atc ccc ggc aag agg agt gaa agg ttc tat gag tgc   739
Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg Phe Tyr Glu Cys
            200                 205                 210

tgc aaa gag ccc tac ccc gat gtc acc ttc aca gtg acc atg cgc cgc   787
Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val Thr Met Arg Arg
        215                 220                 225

agg aca ctc tac tat ggc ctc aac ctg ctg atc ccc tgt gtg ctc atc   835
Arg Thr Leu Tyr Tyr Gly Leu Asn Leu Leu Ile Pro Cys Val Leu Ile
    230                 235                 240

tcc gcc ctc gcc ctg ctg gtg ttc ctg ctt cct gca gat tcc ggg gag   883
Ser Ala Leu Ala Leu Leu Val Phe Leu Leu Pro Ala Asp Ser Gly Glu
245                 250                 255                 260

aag att tcc ctg ggg ata aca gtc tta ctc tct ctt acc gtc ttc atg   931
Lys Ile Ser Leu Gly Ile Thr Val Leu Leu Ser Leu Thr Val Phe Met
                265                 270                 275

ctg ctc gtg gct gag atc atg ccc gca aca tcc gat tcg gta cca ttg   979
Leu Leu Val Ala Glu Ile Met Pro Ala Thr Ser Asp Ser Val Pro Leu
            280                 285                 290

ata gcc cag tac ttc gcc agc acc atg atc atc gtg ggc ctc tcg gtg   1027
Ile Ala Gln Tyr Phe Ala Ser Thr Met Ile Ile Val Gly Leu Ser Val
        295                 300                 305

gtg gtg aca gtg atc gtg ctg cag tac cac cac cac gac ccc gac ggg   1075
Val Val Thr Val Ile Val Leu Gln Tyr His His His Asp Pro Asp Gly
    310                 315                 320

ggc aag atg ccc aag tgg acc aga gtc atc ctt ctg aac tgg tgc gcg   1123
Gly Lys Met Pro Lys Trp Thr Arg Val Ile Leu Leu Asn Trp Cys Ala
325                 330                 335                 340

tgg ttc ctg cga atg aag agg ccc ggg gag gac aag gtg cgc ccg gcc   1171
Trp Phe Leu Arg Met Lys Arg Pro Gly Glu Asp Lys Val Arg Pro Ala
                345                 350                 355

tgc cag cac aag cag cgg cgc tgc agc ctg gcc agt gtg gag atg agc   1219
Cys Gln His Lys Gln Arg Arg Cys Ser Leu Ala Ser Val Glu Met Ser
            360                 365                 370

gcc gtg ggc ccg ccg ccc gcc agc aac ggg aac ctg ctg tac atc ggc   1267
Ala Val Gly Pro Pro Pro Ala Ser Asn Gly Asn Leu Leu Tyr Ile Gly
        375                 380                 385

ttc cgc ggc ctg gac ggc gtg cac tgt gtc ccg acc ccc gac tct ggg   1315
Phe Arg Gly Leu Asp Gly Val His Cys Val Pro Thr Pro Asp Ser Gly
    390                 395                 400

gta gtg tgt ggc cgc atg gcc tgc tcc ccc acg cac gat gag cac ctc   1363
Val Val Cys Gly Arg Met Ala Cys Ser Pro Thr His Asp Glu His Leu
405                 410                 415                 420

ctg cac ggc ggg caa ccc ccc gag ggg gac ccg gac ttg gcc aag atc   1411
Leu His Gly Gly Gln Pro Pro Glu Gly Asp Pro Asp Leu Ala Lys Ile
                425                 430                 435

ctg gag gag gtc cgc tac att gcc aac cgc ttc cgc tgc cag gac gaa   1459
```

```
Leu Glu Glu Val Arg Tyr Ile Ala Asn Arg Phe Arg Cys Gln Asp Glu
            440                 445                 450

agc gag gcg gtc tgc agc gag tgg aag ttc gcc gcc tgt gtg gtg gac   1507
Ser Glu Ala Val Cys Ser Glu Trp Lys Phe Ala Ala Cys Val Val Asp
        455                 460                 465

cgc ctg tgc ctc atg gcc ttc tcg gtc ttc acc atc atc tgc acc atc   1555
Arg Leu Cys Leu Met Ala Phe Ser Val Phe Thr Ile Ile Cys Thr Ile
    470                 475                 480

ggc atc ctg atg tcg gct ccc aac ttc gtg gag gcc gtg tcc aaa gac   1603
Gly Ile Leu Met Ser Ala Pro Asn Phe Val Glu Ala Val Ser Lys Asp
485                 490                 495                 500

ttt gcg taa ccacactggt tctgtacatg tggaaaactc acagatgggc           1652
Phe Ala  *


aaggcctttg gcttggcgag atttgggggt gctaatccag gacagcatta cacgccacaa 1712
ctccagtgtt cccttctggc tgtcagtcgt gttgcttacg gtttctttgt tactttaggt 1772
agtagaatct cagcactttg tttcatattc tcagatgggc tgatagatac tccttggcac 1832
atccgtacca tcggtcagca gggccactga gtagtcattt tgccattagc cctcagcctg 1892
gaaagccctt cggagagctc cccatggctc ctcaccaccg agacagttgg ttttgcatgt 1952
ctgcatgaag gtctacctga aaattcaaca tttgcttttt gcttgtgtac aaacccagat 2012
tgaagctaaa ataaaccaga ctcactaaat cctttccaat aattgactgg tggaaggaaa 2072
acaaaaaaaa aaaaa                                                  2087

<210> 8
<211> 502
<212> PRT
<213> Homo sapiens

<400> 8
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Gly Leu Ala Ala Ser Leu
 1               5                  10                  15
Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30
Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45
Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60
Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80
Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95
Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110
Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125
Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140
Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160
Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175
Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190
Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205
Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
```

```
    210                 215                 220
Thr Met Arg Arg Arg Thr Leu Tyr Tyr Gly Leu Asn Leu Leu Ile Pro
225                 230                 235                 240
Cys Val Leu Ile Ser Ala Leu Ala Leu Leu Val Phe Leu Leu Pro Ala
                245                 250                 255
Asp Ser Gly Glu Lys Ile Ser Leu Gly Ile Thr Val Leu Leu Ser Leu
            260                 265                 270
Thr Val Phe Met Leu Leu Val Ala Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285
Ser Val Pro Leu Ile Ala Gln Tyr Phe Ala Ser Thr Met Ile Ile Val
    290                 295                 300
Gly Leu Ser Val Val Val Thr Val Ile Val Leu Gln Tyr His His His
305                 310                 315                 320
Asp Pro Asp Gly Gly Lys Met Pro Lys Trp Thr Arg Val Ile Leu Leu
                325                 330                 335
Asn Trp Cys Ala Trp Phe Leu Arg Met Lys Arg Pro Gly Glu Asp Lys
            340                 345                 350
Val Arg Pro Ala Cys Gln His Lys Gln Arg Arg Cys Ser Leu Ala Ser
        355                 360                 365
Val Glu Met Ser Ala Val Gly Pro Pro Pro Ala Ser Asn Gly Asn Leu
    370                 375                 380
Leu Tyr Ile Gly Phe Arg Gly Leu Asp Gly Val His Cys Val Pro Thr
385                 390                 395                 400
Pro Asp Ser Gly Val Val Cys Gly Arg Met Ala Cys Ser Pro Thr His
                405                 410                 415
Asp Glu His Leu Leu His Gly Gly Gln Pro Pro Glu Gly Asp Pro Asp
            420                 425                 430
Leu Ala Lys Ile Leu Glu Glu Val Arg Tyr Ile Ala Asn Arg Phe Arg
        435                 440                 445
Cys Gln Asp Glu Ser Glu Ala Val Cys Ser Glu Trp Lys Phe Ala Ala
    450                 455                 460
Cys Val Val Asp Arg Leu Cys Leu Met Ala Phe Ser Val Phe Thr Ile
465                 470                 475                 480
Ile Cys Thr Ile Gly Ile Leu Met Ser Ala Pro Asn Phe Val Glu Ala
                485                 490                 495
Val Ser Lys Asp Phe Ala
            500
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<210> 9
<211> 2585
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (248)...(1825)

<400> 9

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agccccgggg cgccgcgcgg agagcaagcg gagatagcga ctttgcgccc cccagccctc 180
gccttcttgc atcgcgttcc ccgcatcctc gggtccttct gtcctttccg ctgtccccac 240
cgccgcc atg gcc acc ttg ctc cgc agc aag ctg tcc aac gtg gcc acg   289
       Met Ala Thr Leu Leu Arg Ser Lys Leu Ser Asn Val Ala Thr
        1               5                   10

tcc gtg tcc aac aag tcc cag gcc aag atg agc ggc atg ttc gcc agg   337
Ser Val Ser Asn Lys Ser Gln Ala Lys Met Ser Gly Met Phe Ala Arg
 15                  20                  25                  30
```

```
atg ggt ttt cag gcg gcc acg gat gag gag gcg gtg ggc ttc gcg cat   385
Met Gly Phe Gln Ala Ala Thr Asp Glu Glu Ala Val Gly Phe Ala His
                35                  40                  45

tgc gac gac ctc gac ttt gag cac cgc cag ggc ctg cag atg gac atc   433
Cys Asp Asp Leu Asp Phe Glu His Arg Gln Gly Leu Gln Met Asp Ile
            50                  55                  60

ctg aaa gcc gag gga gag ccc tgc ggg gac gag ggc gct gaa gcg ccc   481
Leu Lys Ala Glu Gly Glu Pro Cys Gly Asp Glu Gly Ala Glu Ala Pro
        65                  70                  75

gtc gag gga gac atc cat tat cag cga ggc agc gga gct cct ctg ccg   529
Val Glu Gly Asp Ile His Tyr Gln Arg Gly Ser Gly Ala Pro Leu Pro
    80                  85                  90

ccc tcc ggc tcc aag gac cag gtg gga ggt ggt ggc gaa ttc ggg ggc   577
Pro Ser Gly Ser Lys Asp Gln Val Gly Gly Gly Gly Glu Phe Gly Gly
95                  100                 105                 110

cac gac aag ccc aaa atc acg gcg tgg gag gca ggc tgg aac gtg acc   625
His Asp Lys Pro Lys Ile Thr Ala Trp Glu Ala Gly Trp Asn Val Thr
                115                 120                 125

aac gcc atc cag ggc atg ttc gtg ctg ggc cta ccc tac gcc atc ctg   673
Asn Ala Ile Gln Gly Met Phe Val Leu Gly Leu Pro Tyr Ala Ile Leu
            130                 135                 140

cac ggc ggc tac ctg ggg ttg ttt ctc atc atc ttc gcc gcc gtt gtg   721
His Gly Gly Tyr Leu Gly Leu Phe Leu Ile Ile Phe Ala Ala Val Val
        145                 150                 155

tgc tgc tac acc ggc aag atc ctc atc gcg tgc ctg tac gag gag aat   769
Cys Cys Tyr Thr Gly Lys Ile Leu Ile Ala Cys Leu Tyr Glu Glu Asn
    160                 165                 170

gaa gac ggc gag gtg gtg cgc gtg cgg gac tcg tac gtg gcc ata gcc   817
Glu Asp Gly Glu Val Val Arg Val Arg Asp Ser Tyr Val Ala Ile Ala
175                 180                 185                 190

aac gcc tgc tgc gcc ccg cgc ttc cca acg ctg ggc ggc cga gtg gtg   865
Asn Ala Cys Cys Ala Pro Arg Phe Pro Thr Leu Gly Gly Arg Val Val
                195                 200                 205

aac gta gcg cag atc atc gag ctg gtg atg acg tgc atc ctg tac gtg   913
Asn Val Ala Gln Ile Ile Glu Leu Val Met Thr Cys Ile Leu Tyr Val
            210                 215                 220

gtg gtg agt ggc aac ctc atg tac aac agc ttc ccg ggg ctg ccc gtg   961
Val Val Ser Gly Asn Leu Met Tyr Asn Ser Phe Pro Gly Leu Pro Val
        225                 230                 235

tcg cag aag tcc tgg tcc att atc gcc acg gcc gtg ctg ctg cct tgc   1009
Ser Gln Lys Ser Trp Ser Ile Ile Ala Thr Ala Val Leu Leu Pro Cys
    240                 245                 250

gcc ttc ctt aag aac ctc aag gcc gtg tcc aag ttc agt ctg ctg tgc   1057
Ala Phe Leu Lys Asn Leu Lys Ala Val Ser Lys Phe Ser Leu Leu Cys
255                 260                 265                 270

act ctg gcc cac ttc gtc atc aat atc ctg gtc ata gcc tac tgt cta   1105
```

```
Thr Leu Ala His Phe Val Ile Asn Ile Leu Val Ile Ala Tyr Cys Leu
                275                 280                 285

tcg cgg gcg cgc gac tgg gcc tgg gag aag gtc aag ttc tac atc gac  1153
Ser Arg Ala Arg Asp Trp Ala Trp Glu Lys Val Lys Phe Tyr Ile Asp
            290                 295                 300

gtc aag aag ttc ccc atc tcc att ggc atc atc gtg ttc agc tac acg  1201
Val Lys Lys Phe Pro Ile Ser Ile Gly Ile Ile Val Phe Ser Tyr Thr
        305                 310                 315

tct cag atc ttc ctg cct tcg ctg gag ggc aat atg cag cag ccc agc  1249
Ser Gln Ile Phe Leu Pro Ser Leu Glu Gly Asn Met Gln Gln Pro Ser
    320                 325                 330

gag ttc cac tgc atg atg aac tgg acg cac atc gca gcc tgc gtg ctc  1297
Glu Phe His Cys Met Met Asn Trp Thr His Ile Ala Ala Cys Val Leu
335                 340                 345                 350

aag ggc ctc ttc gcg ctc gtc gcc tac ctc acc tgg gcc gac gag acc  1345
Lys Gly Leu Phe Ala Leu Val Ala Tyr Leu Thr Trp Ala Asp Glu Thr
                355                 360                 365

aag gag gtc atc acg gat aac ctg ccc ggc tcc atc cgc gcc gtg gtc  1393
Lys Glu Val Ile Thr Asp Asn Leu Pro Gly Ser Ile Arg Ala Val Val
            370                 375                 380

aac atc ttt ctg gtg gcc aag gcg ctg ttg tcc tat cct ctg cca ttc  1441
Asn Ile Phe Leu Val Ala Lys Ala Leu Leu Ser Tyr Pro Leu Pro Phe
        385                 390                 395

ttt gcc gct gtc gag gtg ctg gag aag tcg ctc ttc cag gaa ggc agc  1489
Phe Ala Ala Val Glu Val Leu Glu Lys Ser Leu Phe Gln Glu Gly Ser
    400                 405                 410

cgc gcc ttt ttc ccg gcc tgc tac agc ggc gac ggg cgc ctg aag tcc  1537
Arg Ala Phe Phe Pro Ala Cys Tyr Ser Gly Asp Gly Arg Leu Lys Ser
415                 420                 425                 430

tgg ggg ctg acg ctg cgc tgc gcg ctc gtc gtc ttc acg ctg ctc atg  1585
Trp Gly Leu Thr Leu Arg Cys Ala Leu Val Val Phe Thr Leu Leu Met
                435                 440                 445

gcc att tat gtg ccg cac ttc gcg ctg ctc atg ggc ctc acc ggc agc  1633
Ala Ile Tyr Val Pro His Phe Ala Leu Leu Met Gly Leu Thr Gly Ser
            450                 455                 460

ctc acg ggc gcc ggc ctc tgt ttc ttg ctg ccc agc ctc ttt cac ctg  1681
Leu Thr Gly Ala Gly Leu Cys Phe Leu Leu Pro Ser Leu Phe His Leu
        465                 470                 475

cgc ctg ctc tgg cgc aag ctg ctg tgg cac caa gtc ttc ttc gac gtc  1729
Arg Leu Leu Trp Arg Lys Leu Leu Trp His Gln Val Phe Phe Asp Val
    480                 485                 490

gcc atc ttc gtc atc ggc ggc atc tgc agc gtg tcc ggc ttc gtg cac  1777
Ala Ile Phe Val Ile Gly Gly Ile Cys Ser Val Ser Gly Phe Val His
495                 500                 505                 510

tcc ctc gag ggc ctc atc gaa gcc tac cga acc aac gcg gag gac tag  1825
Ser Leu Glu Gly Leu Ile Glu Ala Tyr Arg Thr Asn Ala Glu Asp  *
```

515 520 525

ggcgcaaggg cgagcccccg ccgcgcttct gcgctctctc ccttctcccc tcaccccgcc 1885
cccaccagcc cagtgcgccc tgccgccgcg cttgggaggc caagctttaa acatctctgg 1945
ttcctagttt ctgattattc ggggatgggg gggatgggag gggacaggga ttcacgatcc 2005
atcgcgtctg cgtttctgtt gtcctttctt ttccacaaca ccctggtttt ggggggaggc 2065
ggggtgcatt tgcgggcagg gttctctgtc cttccaagtg gggccccgac actttggttc 2125
cagtcatcga gggggttggg aagggaggga gaggggggcgc agctcgcagg cgtggcaact 2185
tgaccttggg ggaatatttc acatccatcc agagctcgga atctacagcg tccagccatt 2245
tccagcaaga gcgcttccca ttccggagac gtttcaaccc tgcagcggga aaggctgact 2305
gggaaatcca ttttgggtgg gcaatttcct tcaacgaagc cggaaggcga gaagccgcgg 2365
cggggccagc ttgcctgccg gttttcagga atctaaactc tcatcttgtg caatttatca 2425
ggtgtggaac tgttctactg tgcgtgtggt gtgctcgtgg tgaataagat gaaatgtata 2485
tcagaaaaaa atctatctct aatttagagt gcggtacata attatatccg caaataaaga 2545
agagacaaag gcttgaaaaa aaaaaaaaaa aaaaaaaaaa 2585

<210> 10
<211> 525
<212> PRT
<213> Homo sapiens

<400> 10
Met Ala Thr Leu Leu Arg Ser Lys Leu Ser Asn Val Ala Thr Ser Val
1 5 10 15
Ser Asn Lys Ser Gln Ala Lys Met Ser Gly Met Phe Ala Arg Met Gly
20 25 30
Phe Gln Ala Ala Thr Asp Glu Glu Ala Val Gly Phe Ala His Cys Asp
35 40 45
Asp Leu Asp Phe Glu His Arg Gln Gly Leu Gln Met Asp Ile Leu Lys
50 55 60
Ala Glu Gly Glu Pro Cys Gly Asp Glu Gly Ala Glu Ala Pro Val Glu
65 70 75 80
Gly Asp Ile His Tyr Gln Arg Gly Ser Gly Ala Pro Leu Pro Pro Ser
85 90 95
Gly Ser Lys Asp Gln Val Gly Gly Gly Gly Glu Phe Gly Gly His Asp
100 105 110
Lys Pro Lys Ile Thr Ala Trp Glu Ala Gly Trp Asn Val Thr Asn Ala
115 120 125
Ile Gln Gly Met Phe Val Leu Gly Leu Pro Tyr Ala Ile Leu His Gly
130 135 140
Gly Tyr Leu Gly Leu Phe Leu Ile Ile Phe Ala Ala Val Val Cys Cys
145 150 155 160
Tyr Thr Gly Lys Ile Leu Ile Ala Cys Leu Tyr Glu Glu Asn Glu Asp
165 170 175
Gly Glu Val Val Arg Val Arg Asp Ser Tyr Val Ala Ile Ala Asn Ala
180 185 190
Cys Cys Ala Pro Arg Phe Pro Thr Leu Gly Gly Arg Val Val Asn Val
195 200 205
Ala Gln Ile Ile Glu Leu Val Met Thr Cys Ile Leu Tyr Val Val Val
210 215 220
Ser Gly Asn Leu Met Tyr Asn Ser Phe Pro Gly Leu Pro Val Ser Gln
225 230 235 240
Lys Ser Trp Ser Ile Ile Ala Thr Ala Val Leu Leu Pro Cys Ala Phe
245 250 255
Leu Lys Asn Leu Lys Ala Val Ser Lys Phe Ser Leu Leu Cys Thr Leu
260 265 270
Ala His Phe Val Ile Asn Ile Leu Val Ile Ala Tyr Cys Leu Ser Arg
275 280 285
Ala Arg Asp Trp Ala Trp Glu Lys Val Lys Phe Tyr Ile Asp Val Lys
290 295 300
Lys Phe Pro Ile Ser Ile Gly Ile Ile Val Phe Ser Tyr Thr Ser Gln

```
305                 310                 315                 320
Ile Phe Leu Pro Ser Leu Glu Gly Asn Met Gln Gln Pro Ser Glu Phe
                325                 330                 335
His Cys Met Met Asn Trp Thr His Ile Ala Ala Cys Val Leu Lys Gly
            340                 345                 350
Leu Phe Ala Leu Val Ala Tyr Leu Thr Trp Ala Asp Glu Thr Lys Glu
        355                 360                 365
Val Ile Thr Asp Asn Leu Pro Gly Ser Ile Arg Ala Val Val Asn Ile
    370                 375                 380
Phe Leu Val Ala Lys Ala Leu Leu Ser Tyr Pro Leu Pro Phe Phe Ala
385                 390                 395                 400
Ala Val Glu Val Leu Glu Lys Ser Leu Phe Gln Glu Gly Ser Arg Ala
                405                 410                 415
Phe Phe Pro Ala Cys Tyr Ser Gly Asp Gly Arg Leu Lys Ser Trp Gly
            420                 425                 430
Leu Thr Leu Arg Cys Ala Leu Val Val Phe Thr Leu Leu Met Ala Ile
        435                 440                 445
Tyr Val Pro His Phe Ala Leu Leu Met Gly Leu Thr Gly Ser Leu Thr
    450                 455                 460
Gly Ala Gly Leu Cys Phe Leu Leu Pro Ser Leu Phe His Leu Arg Leu
465                 470                 475                 480
Leu Trp Arg Lys Leu Leu Trp His Gln Val Phe Phe Asp Val Ala Ile
                485                 490                 495
Phe Val Ile Gly Gly Ile Cys Ser Val Ser Gly Phe Val His Ser Leu
            500                 505                 510
Glu Gly Leu Ile Glu Ala Tyr Arg Thr Asn Ala Glu Asp
        515                 520                 525
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<210> 11
<211> 1062
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1062)

<400> 11

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atg gaa acc aac ttc tcc att cct ctg aat gaa act gag gag gtg ctc   48
Met Glu Thr Asn Phe Ser Ile Pro Leu Asn Glu Thr Glu Glu Val Leu
 1               5                  10                  15

cct gag cct gct ggc cac acc gtt ctg tgg atc ttc tca ttg cta gtc   96
Pro Glu Pro Ala Gly His Thr Val Leu Trp Ile Phe Ser Leu Leu Val
            20                  25                  30

cac gga gtc acc ttt gtc ttc ggg gtc ctg ggc aat ggg ctt gtg atc   144
His Gly Val Thr Phe Val Phe Gly Val Leu Gly Asn Gly Leu Val Ile
        35                  40                  45

tgg gtg gct gga ttc cgg atg aca cgc aca gtc aac acc atc tgt tac   192
Trp Val Ala Gly Phe Arg Met Thr Arg Thr Val Asn Thr Ile Cys Tyr
    50                  55                  60

ctg aac ctg gcc cta gct gac ttc tct ttc agt gcc atc cta cca ttc   240
Leu Asn Leu Ala Leu Ala Asp Phe Ser Phe Ser Ala Ile Leu Pro Phe
65                  70                  75                  80

cga atg gtc tca gtc gcc atg aga gaa aaa tgg cct ttt gcg tca ttc   288
Arg Met Val Ser Val Ala Met Arg Glu Lys Trp Pro Phe Ala Ser Phe
```

```
                85                  90                  95

cta tgt aag tta gtt cat gtt atg ata gac atc aac ctg ttt gtc agt   336
Leu Cys Lys Leu Val His Val Met Ile Asp Ile Asn Leu Phe Val Ser
            100                 105                 110

gtc tac ctg atc acc atc att gct ctg gac cgc tgt att tgt gtc ctg   384
Val Tyr Leu Ile Thr Ile Ile Ala Leu Asp Arg Cys Ile Cys Val Leu
        115                 120                 125

cat cca gcc tgg gcc cag aac cat cgc acc atg agt ctg gcc aag agg   432
His Pro Ala Trp Ala Gln Asn His Arg Thr Met Ser Leu Ala Lys Arg
    130                 135                 140

gtg atg acg gga ctc tgg att ttc acc ata gtc ctt acc tta cca aat   480
Val Met Thr Gly Leu Trp Ile Phe Thr Ile Val Leu Thr Leu Pro Asn
145                 150                 155                 160

ttc atc ttc tgg act aca ata agt act acg aat ggg gac aca tac tgt   528
Phe Ile Phe Trp Thr Thr Ile Ser Thr Thr Asn Gly Asp Thr Tyr Cys
                165                 170                 175

att ttc aac ttt gca ttc tgg ggt gac act gct gta gag agg ttg aac   576
Ile Phe Asn Phe Ala Phe Trp Gly Asp Thr Ala Val Glu Arg Leu Asn
            180                 185                 190

gtg ttc att acc atg gcc aag gtc ttt ctg atc ctc cac ttc att att   624
Val Phe Ile Thr Met Ala Lys Val Phe Leu Ile Leu His Phe Ile Ile
        195                 200                 205

ggc ttc acg gtg cct atg tcc atc atc aca gtc tgc tat ggg atc atc   672
Gly Phe Thr Val Pro Met Ser Ile Ile Thr Val Cys Tyr Gly Ile Ile
    210                 215                 220

gct gcc aaa att cac aga aac cac atg att aaa tcc agc cgt ccc tta   720
Ala Ala Lys Ile His Arg Asn His Met Ile Lys Ser Ser Arg Pro Leu
225                 230                 235                 240

cgt gtc ttc gct gct gtg gtg gct tct ttc ttc atc tgt tgg ttc cct   768
Arg Val Phe Ala Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro
                245                 250                 255

tat gaa cta att ggc att cta atg gca gtc tgg ctc aaa gag atg ttg   816
Tyr Glu Leu Ile Gly Ile Leu Met Ala Val Trp Leu Lys Glu Met Leu
            260                 265                 270

tta aat ggc aaa tac aaa atc att ctt gtc ctg att aac cca aca agc   864
Leu Asn Gly Lys Tyr Lys Ile Ile Leu Val Leu Ile Asn Pro Thr Ser
        275                 280                 285

tcc ttg gcc ttt ttt aac agc tgc ctc aac cca att ctc tac gtc ttt   912
Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Ile Leu Tyr Val Phe
    290                 295                 300

atg ggt cgt aac ttc caa gaa aga ctg att cgc tct ttg ccc act agt   960
Met Gly Arg Asn Phe Gln Glu Arg Leu Ile Arg Ser Leu Pro Thr Ser
305                 310                 315                 320

ttg gag agg gcc ctg act gag gtc cct gac tca gcc cag acc agc aac  1008
Leu Glu Arg Ala Leu Thr Glu Val Pro Asp Ser Ala Gln Thr Ser Asn
                325                 330                 335
```

```
aca cac acc act tct gct tca cct cct gag gag acg gag tta caa gca   1056
Thr His Thr Thr Ser Ala Ser Pro Pro Glu Glu Thr Glu Leu Gln Ala
            340                 345                 350

atg tga                                                           1062
Met  *
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<210> 12
<211> 353
<212> PRT
<213> Homo sapiens

<400> 12

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Met Glu Thr Asn Phe Ser Ile Pro Leu Asn Glu Thr Glu Glu Val Leu
 1               5                  10                  15
Pro Glu Pro Ala Gly His Thr Val Leu Trp Ile Phe Ser Leu Leu Val
            20                  25                  30
His Gly Val Thr Phe Val Phe Gly Val Leu Gly Asn Gly Leu Val Ile
        35                  40                  45
Trp Val Ala Gly Phe Arg Met Thr Arg Thr Val Asn Thr Ile Cys Tyr
    50                  55                  60
Leu Asn Leu Ala Leu Ala Asp Phe Ser Phe Ser Ala Ile Leu Pro Phe
65                  70                  75                  80
Arg Met Val Ser Val Ala Met Arg Glu Lys Trp Pro Phe Ala Ser Phe
                85                  90                  95
Leu Cys Lys Leu Val His Val Met Ile Asp Ile Asn Leu Phe Val Ser
            100                 105                 110
Val Tyr Leu Ile Thr Ile Ile Ala Leu Asp Arg Cys Ile Cys Val Leu
        115                 120                 125
His Pro Ala Trp Ala Gln Asn His Arg Thr Met Ser Leu Ala Lys Arg
    130                 135                 140
Val Met Thr Gly Leu Trp Ile Phe Thr Ile Val Leu Thr Leu Pro Asn
145                 150                 155                 160
Phe Ile Phe Trp Thr Thr Ile Ser Thr Thr Asn Gly Asp Thr Tyr Cys
                165                 170                 175
Ile Phe Asn Phe Ala Phe Trp Gly Asp Thr Ala Val Glu Arg Leu Asn
            180                 185                 190
Val Phe Ile Thr Met Ala Lys Val Phe Leu Ile Leu His Phe Ile Ile
        195                 200                 205
Gly Phe Thr Val Pro Met Ser Ile Ile Thr Val Cys Tyr Gly Ile Ile
    210                 215                 220
Ala Ala Lys Ile His Arg Asn His Met Ile Lys Ser Ser Arg Pro Leu
225                 230                 235                 240
Arg Val Phe Ala Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro
                245                 250                 255
Tyr Glu Leu Ile Gly Ile Leu Met Ala Val Trp Leu Lys Glu Met Leu
            260                 265                 270
Leu Asn Gly Lys Tyr Lys Ile Ile Leu Val Leu Ile Asn Pro Thr Ser
        275                 280                 285
Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Ile Leu Tyr Val Phe
    290                 295                 300
Met Gly Arg Asn Phe Gln Glu Arg Leu Ile Arg Ser Leu Pro Thr Ser
305                 310                 315                 320
Leu Glu Arg Ala Leu Thr Glu Val Pro Asp Ser Ala Gln Thr Ser Asn
                325                 330                 335
Thr His Thr Thr Ser Ala Ser Pro Pro Glu Glu Thr Glu Leu Gln Ala
            340                 345                 350
Met
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<210> 13
<211> 4221
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (51)...(2957)

<400> 13
cagcccgagc ccgagcccga gcccgagccg gcgccaccgc gccccggcc atg gct 56
Met Ala
1

ttt gcc aat ttc cgc cgc atc ctg cgc ctg tct acc ttc gag aag aga 104
Phe Ala Asn Phe Arg Arg Ile Leu Arg Leu Ser Thr Phe Glu Lys Arg
5 10 15

aag tcc cgc gaa tat gag cac gtc cgc cgc gac ctg gac ccc aac gag 152
Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro Asn Glu
20 25 30

gtg tgg gag atc gtg ggc gag ctg ggc gac ggc gcc ttc ggc aag gtt 200
Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly Lys Val
35 40 45 50

tac aag gcc aag aat aag gag acg ggt gct ttg gct gcg gcc aaa gtc 248
Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala Lys Val
55 60 65

att gaa acc aag agt gag gag gag ctg gag gac tac atc gtg gag att 296
Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val Glu Ile
70 75 80

gag atc ctg gcc acc tgc gac cac ccc tac att gtg aag ctc ctg gga 344
Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu Leu Gly
85 90 95

gcc tac tat cac gac ggg aag ctg tgg atc atg att gag ttc tgt cca 392
Ala Tyr Tyr His Asp Gly Lys Leu Trp Ile Met Ile Glu Phe Cys Pro
100 105 110

ggg gga gcc gtg gac gcc atc atg ctg gag ctg gac aga ggc ctc acg 440
Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly Leu Thr
115 120 125 130

gag ccc cag ata cag gtg gtt tgc cgc cag atg cta gaa gcc ctc aac 488
Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala Leu Asn
135 140 145

ttc ctg cac agc aag agg atc atc cac cga gat ctg aaa gct ggc aac 536
Phe Leu His Ser Lys Arg Ile Ile His Arg Asp Leu Lys Ala Gly Asn
150 155 160

gtg ctg atg acc ctc gag gga gac atc agg ctg gct gac ttt ggt gtg 584
Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe Gly Val
165 170 175

```
tct gcc aag aat ctg aag act cta cag aaa cga gat tcc ttc atc ggc   632
Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe Ile Gly
    180                 185                 190

acg cct tac tgg atg gcc ccc gag gtg gtc atg tgt gag acc atg aaa   680
Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr Met Lys
195                 200                 205                 210

gac acg ccc tac gac tac aaa gcc gac atc tgg tcc ctg ggc atc acg   728
Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr
                215                 220                 225

ctg att gag atg gcc cag atc gag ccg cca cac cac gag ctc aac ccc   776
Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu Asn Pro
            230                 235                 240

atg cgg gtc ctg cta aag atc gcc aag tca gac cct ccc acg ctg ctc   824
Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr Leu Leu
        245                 250                 255

acg ccc tcc aag tgg tct gta gag ttc cgt gac ttc ctg aag ata gcc   872
Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys Ile Ala
    260                 265                 270

ctg gat aag aac cca gaa acc cga ccc agt gcc gcg cag ctg ctg gag   920
Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu Leu Glu
275                 280                 285                 290

cat ccc ttc gtc agc agc atc acc agt aac aag gct ctg cgg gag ctg   968
His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg Glu Leu
                295                 300                 305

gtg gct gag gcc aag gcc gag gtg atg gaa gag atc gaa gac ggc cgg   1016
Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp Gly Arg
            310                 315                 320

gat gag ggg gaa gag gag gac gcc gtg gat gcc gcc tcc acc ctg gag   1064
Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr Leu Glu
        325                 330                 335

aac cat act cag aac tcc tct gag gtg agt ccg cca agc ctc aat gct   1112
Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu Asn Ala
    340                 345                 350

gac aag cct ctc gag gag tca cct tcc acc ccg ctg gca ccc agc cag   1160
Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro Ser Gln
355                 360                 365                 370

tct cag gac agt gtg aat gag ccc tgc agc cag ccc tct ggg gac aga   1208
Ser Gln Asp Ser Val Asn Glu Pro Cys Ser Gln Pro Ser Gly Asp Arg
                375                 380                 385

tcc ctc caa acc acc agt ccc cca gtc gtg gcc cct gga aat gag aac   1256
Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn Glu Asn
            390                 395                 400

ggc ctg gca gtg cct gtg ccc ctg cgg aag tcc cga ccc gtg tca atg   1304
Gly Leu Ala Val Pro Val Pro Leu Arg Lys Ser Arg Pro Val Ser Met
        405                 410                 415

gat gcc aga att cag gta gcc cag gag aag caa gtt gct gag cag ggt   1352
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Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu Gln Gly
    420                 425                 430

ggg gac ctc agc cca gca gcc aac aga tct caa aag gcc agc cag agc   1400
Gly Asp Leu Ser Pro Ala Ala Asn Arg Ser Gln Lys Ala Ser Gln Ser
435                 440                 445                 450

cgg ccc aac agc agc gcc ctg gag acc ttg ggt ggg gag aag ctg gcc   1448
Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Lys Leu Ala
                455                 460                 465

aat ggc agc ctg gag cca cct gcc cag gca gct cca ggg cct tcc aag   1496
Asn Gly Ser Leu Glu Pro Pro Ala Gln Ala Ala Pro Gly Pro Ser Lys
            470                 475                 480

agg gac tcg gac tgc agc agc ctc tgc acc tct gag agc atg gac tat   1544
Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met Asp Tyr
        485                 490                 495

ggt acc aat ctc tcc act gac ctg tcg ctg aac aaa gag atg ggc tct   1592
Gly Thr Asn Leu Ser Thr Asp Leu Ser Leu Asn Lys Glu Met Gly Ser
    500                 505                 510

ctg tcc atc aag gac ccg aaa ctg tac aaa aaa acc ctc aag cgg aca   1640
Leu Ser Ile Lys Asp Pro Lys Leu Tyr Lys Lys Thr Leu Lys Arg Thr
515                 520                 525                 530

cgc aaa ttt gtg gtg gat ggt gtg gag gtg agc atc acc acc tcc aag   1688
Arg Lys Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr Ser Lys
                535                 540                 545

atc atc agc gaa gat gag aag aag gat gag gag atg aga ttt ctc agg   1736
Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe Leu Arg
            550                 555                 560

cgc cag gaa ctc cga gag ctt cgg ctg ctc cag aaa gaa gag cat cgg   1784
Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu His Arg
        565                 570                 575

aac cag acc cag ctg agt aac aag cat gag ctg cag ctg gag caa atg   1832
Asn Gln Thr Gln Leu Ser Asn Lys His Glu Leu Gln Leu Glu Gln Met
    580                 585                 590

cat aaa cgt ttt gaa cag gaa atc aac gcc aag aag aag ttc ttt gac   1880
His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe Phe Asp
595                 600                 605                 610

acg gaa tta gag aac ctg gag cgt cag caa aag cag caa gtg gag aag   1928
Thr Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val Glu Lys
                615                 620                 625

atg gag caa gac cat gcc gtg cgc cgc cgg gag gag gcc agg cgg atc   1976
Met Glu Gln Asp His Ala Val Arg Arg Arg Glu Glu Ala Arg Arg Ile
            630                 635                 640

cgc ctg gag cag gat cgg gac tac acc agg ttc caa gag cag ctc aaa   2024
Arg Leu Glu Gln Asp Arg Asp Tyr Thr Arg Phe Gln Glu Gln Leu Lys
        645                 650                 655

ctg atg aag aaa gag gtg aag aac gag gtg gag aag ctc ccc cga cag   2072
Leu Met Lys Lys Glu Val Lys Asn Glu Val Glu Lys Leu Pro Arg Gln
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    660                 665                 670

cag cgg aag gaa agc atg aag cag aag atg gag gag cac acg cag aaa   2120
Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr Gln Lys
675                 680                 685                 690

aag cag ctt ctt gac cgg gac ttt gta gcc aag cag aag gag gac ctg   2168
Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu Asp Leu
                695                 700                 705

gag ctg gcc atg aag agg ctc acc acc gac aac agg cgg gag atc tgt   2216
Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu Ile Cys
            710                 715                 720

gac aag gag cgc gag tgc ctc atg aag aag cag gag ctc ctt cga gac   2264
Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu Arg Asp
        725                 730                 735

cgg gaa gca gcc ctg tgg gag atg gaa gag cac cag ctg cag gag agg   2312
Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln Glu Arg
    740                 745                 750

cac cag ctg gtg aag cag cag ctc aaa gac cag tac ttc ctc cag cgg   2360
His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu Gln Arg
755                 760                 765                 770

cac gag ctg ctg cgc aag cat gag aag gag cgg gag cag atg cag cgc   2408
His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met Gln Arg
                775                 780                 785

tac aac cag cgc atg ata gag cag ctg aag gtg cgg cag caa cag gaa   2456
Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln Gln Glu
            790                 795                 800

aag gcg cgg ctg ccc aag atc cag agg agt gag ggc aag acg cgc atg   2504
Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr Arg Met
        805                 810                 815

gcc atg tac aag aag agc ctc cac atc aac ggc ggg ggc agc gca gct   2552
Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser Ala Ala
    820                 825                 830

gag cag cgt gag aag atc aag cag ttc tcc cag cag gag gag aag agg   2600
Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu Lys Arg
835                 840                 845                 850

cag aag tcg gag cgg ctg cag caa cag cag aaa cac gag aac cag atg   2648
Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn Gln Met
                855                 860                 865

cgg gac atg ctg gcg cag tgt gag agc aac atg agc gag ctg cag cag   2696
Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu Gln Gln
            870                 875                 880

ctg cag aat gaa aag tgc cac ctc ctg gta gag cac gaa acc cag aaa   2744
Leu Gln Asn Glu Lys Cys His Leu Leu Val Glu His Glu Thr Gln Lys
        885                 890                 895

ctg aag gcc ctg gat gag agc cat aac cag aac ctg aag gaa tgg cgg   2792
Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu Trp Arg
    900                 905                 910
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gac aag ctt cgg ccg cgc aag aag gct ctg gaa gag gat ctg aac cag   2840
Asp Lys Leu Arg Pro Arg Lys Lys Ala Leu Glu Glu Asp Leu Asn Gln
915                 920                 925                 930

aag aag cgg gag cag gag atg ttc ttc aag ctg agc gag gag gcg gag   2888
Lys Lys Arg Glu Gln Glu Met Phe Phe Lys Leu Ser Glu Glu Ala Glu
                935                 940                 945

tgc cca aac ccc tcc acc cca agc aag gcc gcc aag ttc ttc ccc tac   2936
Cys Pro Asn Pro Ser Thr Pro Ser Lys Ala Ala Lys Phe Phe Pro Tyr
            950                 955                 960

agt tct gcg gat gct tct taa caaccgcccg gggctgtggc tggcagcttg      2987
Ser Ser Ala Asp Ala Ser  *
        965

gtgggcccca gggccttctc cttcattctc tgtgaacatg taactcagga ccccttttcc 3047
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atataacaca ataaaagcaa atgtttgaac cagt                             4221
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<212> PRT
<213> Homo sapiens

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 1               5                  10                  15
Lys Arg Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro
            20                  25                  30
Asn Glu Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly
        35                  40                  45
Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala
    50                  55                  60
Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val
65                  70                  75                  80
Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu
                85                  90                  95
Leu Gly Ala Tyr Tyr His Asp Gly Lys Leu Trp Ile Met Ile Glu Phe
            100                 105                 110
Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly
        115                 120                 125
```

```
Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala
    130                 135                 140
Leu Asn Phe Leu His Ser Lys Arg Ile Ile His Arg Asp Leu Lys Ala
145                 150                 155                 160
Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe
                165                 170                 175
Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe
            180                 185                 190
Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr
        195                 200                 205
Met Lys Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly
    210                 215                 220
Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu
225                 230                 235                 240
Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr
                245                 250                 255
Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys
            260                 265                 270
Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu
        275                 280                 285
Leu Glu His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg
    290                 295                 300
Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp
305                 310                 315                 320
Gly Arg Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr
                325                 330                 335
Leu Glu Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu
            340                 345                 350
Asn Ala Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro
        355                 360                 365
Ser Gln Ser Gln Asp Ser Val Asn Glu Pro Cys Ser Gln Pro Ser Gly
    370                 375                 380
Asp Arg Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn
385                 390                 395                 400
Glu Asn Gly Leu Ala Val Pro Val Pro Leu Arg Lys Ser Arg Pro Val
                405                 410                 415
Ser Met Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu
            420                 425                 430
Gln Gly Gly Asp Leu Ser Pro Ala Ala Asn Arg Ser Gln Lys Ala Ser
        435                 440                 445
Gln Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Lys
    450                 455                 460
Leu Ala Asn Gly Ser Leu Glu Pro Pro Ala Gln Ala Ala Pro Gly Pro
465                 470                 475                 480
Ser Lys Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met
                485                 490                 495
Asp Tyr Gly Thr Asn Leu Ser Thr Asp Leu Ser Leu Asn Lys Glu Met
            500                 505                 510
Gly Ser Leu Ser Ile Lys Asp Pro Lys Leu Tyr Lys Lys Thr Leu Lys
        515                 520                 525
Arg Thr Arg Lys Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr
    530                 535                 540
Ser Lys Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe
545                 550                 555                 560
Leu Arg Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu
                565                 570                 575
His Arg Asn Gln Thr Gln Leu Ser Asn Lys His Glu Leu Gln Leu Glu
            580                 585                 590
Gln Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe
        595                 600                 605
Phe Asp Thr Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val
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```
    610                 615                 620
Glu Lys Met Glu Gln Asp His Ala Val Arg Arg Arg Glu Glu Ala Arg
625                 630                 635                 640
Arg Ile Arg Leu Glu Gln Asp Arg Asp Tyr Thr Arg Phe Gln Glu Gln
                645                 650                 655
Leu Lys Leu Met Lys Lys Glu Val Lys Asn Glu Val Glu Lys Leu Pro
            660                 665                 670
Arg Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr
        675                 680                 685
Gln Lys Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu
    690                 695                 700
Asp Leu Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu
705                 710                 715                 720
Ile Cys Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu
                725                 730                 735
Arg Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln
            740                 745                 750
Glu Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu
        755                 760                 765
Gln Arg His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met
    770                 775                 780
Gln Arg Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln
785                 790                 795                 800
Gln Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr
                805                 810                 815
Arg Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser
            820                 825                 830
Ala Ala Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu
        835                 840                 845
Lys Arg Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn
    850                 855                 860
Gln Met Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu
865                 870                 875                 880
Gln Gln Leu Gln Asn Glu Lys Cys His Leu Leu Val Glu His Glu Thr
                885                 890                 895
Gln Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu
            900                 905                 910
Trp Arg Asp Lys Leu Arg Pro Arg Lys Lys Ala Leu Glu Glu Asp Leu
        915                 920                 925
Asn Gln Lys Lys Arg Glu Gln Glu Met Phe Phe Lys Leu Ser Glu Glu
    930                 935                 940
Ala Glu Cys Pro Asn Pro Ser Thr Pro Ser Lys Ala Ala Lys Phe Phe
945                 950                 955                 960
Pro Tyr Ser Ser Ala Asp Ala Ser
                965
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<211> 3513
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<220>
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gcgacagggc gcagaagcgg g atg tac ttc tgt tgg ggc gcc gac tcc agg   111
                        Met Tyr Phe Cys Trp Gly Ala Asp Ser Arg
                         1               5                   10
```

```
gag ctg cag cgc cgg agg acg gcg ggc agc ccc ggg gct gag cta ctg   159
Glu Leu Gln Arg Arg Arg Thr Ala Gly Ser Pro Gly Ala Glu Leu Leu
                15                  20                  25

cag gcg gcc agc ggg gag cgc cac tct ctg ctg ctg ctg acc aac cac   207
Gln Ala Ala Ser Gly Glu Arg His Ser Leu Leu Leu Leu Thr Asn His
            30                  35                  40

agg gtc ctc tcg tgc gga gac aac agc agg ggt cag ctg ggc cgc agg   255
Arg Val Leu Ser Cys Gly Asp Asn Ser Arg Gly Gln Leu Gly Arg Arg
        45                  50                  55

ggc gcg cag cgc ggg gag ctg cca gaa cca att cag gca ttg gaa acc   303
Gly Ala Gln Arg Gly Glu Leu Pro Glu Pro Ile Gln Ala Leu Glu Thr
    60                  65                  70

cta att gtt gat ctc gtg agc tgc ggg aag gag cac tcc ctg gct gtg   351
Leu Ile Val Asp Leu Val Ser Cys Gly Lys Glu His Ser Leu Ala Val
75                  80                  85                  90

tgc cac aaa gga agg gtc ttc gca tgg gga gct ggt tct gaa ggg cag   399
Cys His Lys Gly Arg Val Phe Ala Trp Gly Ala Gly Ser Glu Gly Gln
                95                  100                 105

ctg ggg att gga gaa ttc aag gaa ata agt ttc aca cct aag aaa ata   447
Leu Gly Ile Gly Glu Phe Lys Glu Ile Ser Phe Thr Pro Lys Lys Ile
            110                 115                 120

atg act ctg aat gat ata aaa ata ata caa gtt tcc tgt gga cac tac   495
Met Thr Leu Asn Asp Ile Lys Ile Ile Gln Val Ser Cys Gly His Tyr
        125                 130                 135

cac tcc ctg gca tta tca aaa gat agc caa gtg ttt tcg tgg gga aag   543
His Ser Leu Ala Leu Ser Lys Asp Ser Gln Val Phe Ser Trp Gly Lys
    140                 145                 150

aac agc cat ggg cag ctg ggc ttg ggg aag gag ttc ccc tcc caa gcc   591
Asn Ser His Gly Gln Leu Gly Leu Gly Lys Glu Phe Pro Ser Gln Ala
155                 160                 165                 170

agc ccg cag agg gtg agg tcc ctg gag ggg atc cca ctg gct cag gtg   639
Ser Pro Gln Arg Val Arg Ser Leu Glu Gly Ile Pro Leu Ala Gln Val
                175                 180                 185

gct gcc gga ggg gct cac agc ttt gcc ctg tct ctc tgt ggg act tcg   687
Ala Ala Gly Gly Ala His Ser Phe Ala Leu Ser Leu Cys Gly Thr Ser
            190                 195                 200

ttt ggc tgg gga agt aac agt gcc ggg cag ctg gcc ctc agt ggg cgt   735
Phe Gly Trp Gly Ser Asn Ser Ala Gly Gln Leu Ala Leu Ser Gly Arg
        205                 210                 215

aat gtc cca gtg caa agc aac aag cct ctc tca gtc ggt gca ctg aag   783
Asn Val Pro Val Gln Ser Asn Lys Pro Leu Ser Val Gly Ala Leu Lys
    220                 225                 230

aat cta ggt gtg gtt tat atc agc tgt ggt gat gca cac act gcg gtg   831
Asn Leu Gly Val Val Tyr Ile Ser Cys Gly Asp Ala His Thr Ala Val
235                 240                 245                 250
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```
ctt acc cag gac ggg aaa gtg ttc aca ttt gga gac aat cgc tct gga   879
Leu Thr Gln Asp Gly Lys Val Phe Thr Phe Gly Asp Asn Arg Ser Gly
                255                 260                 265

cag ctg gga tac agc ccc act cct gag aag aga ggt cca caa ctt gtg   927
Gln Leu Gly Tyr Ser Pro Thr Pro Glu Lys Arg Gly Pro Gln Leu Val
            270                 275                 280

gaa aga att gat ggc cta gtt tcg cag ata gat tgt gga agt tat cac   975
Glu Arg Ile Asp Gly Leu Val Ser Gln Ile Asp Cys Gly Ser Tyr His
        285                 290                 295

acc ctg gca tat gtg cac acc act ggt cag gtg gta tct ttt ggt cat  1023
Thr Leu Ala Tyr Val His Thr Thr Gly Gln Val Val Ser Phe Gly His
    300                 305                 310

gga cca agt gac aca agc aag cca act cat ccg gag gcc ctg aca gag  1071
Gly Pro Ser Asp Thr Ser Lys Pro Thr His Pro Glu Ala Leu Thr Glu
315                 320                 325                 330

aac ttt gac att agc tgc ctg att tct gct gaa gac ttc gtg gat gtt  1119
Asn Phe Asp Ile Ser Cys Leu Ile Ser Ala Glu Asp Phe Val Asp Val
                335                 340                 345

caa gtc aaa cac att ttt gct gga aca tat gcc aac ttt gtg aca act  1167
Gln Val Lys His Ile Phe Ala Gly Thr Tyr Ala Asn Phe Val Thr Thr
            350                 355                 360

cat cag gat act agt tcc aca cgt gct ccc ggg aaa acc ctg cca gaa  1215
His Gln Asp Thr Ser Ser Thr Arg Ala Pro Gly Lys Thr Leu Pro Glu
        365                 370                 375

ata agc cga att agc cag tcc atg gca gaa aaa tgg ata gca gtg aaa  1263
Ile Ser Arg Ile Ser Gln Ser Met Ala Glu Lys Trp Ile Ala Val Lys
    380                 385                 390

aga aga agt act gaa cat gaa atg gct aaa agt gaa att aga atg ata  1311
Arg Arg Ser Thr Glu His Glu Met Ala Lys Ser Glu Ile Arg Met Ile
395                 400                 405                 410

ttt tca tct cct gct tgt ctg act gca agt ttt tta aag aaa aga gga  1359
Phe Ser Ser Pro Ala Cys Leu Thr Ala Ser Phe Leu Lys Lys Arg Gly
                415                 420                 425

act gga gaa acg act tcc att gat gtg gac tta gaa atg gca aga gat  1407
Thr Gly Glu Thr Thr Ser Ile Asp Val Asp Leu Glu Met Ala Arg Asp
            430                 435                 440

acc ttc aag aag tta aca aaa aag gaa tgg att tct tcc atg ata act  1455
Thr Phe Lys Lys Leu Thr Lys Lys Glu Trp Ile Ser Ser Met Ile Thr
        445                 450                 455

acg tgt ctc gag gat gat ctg ctc aga gct ctt cca tgc cat tct cca  1503
Thr Cys Leu Glu Asp Asp Leu Leu Arg Ala Leu Pro Cys His Ser Pro
    460                 465                 470

cac caa gaa gct tta tca gtt ttc ctc ctg ctc cca gaa tgt cct gtg  1551
His Gln Glu Ala Leu Ser Val Phe Leu Leu Leu Pro Glu Cys Pro Val
475                 480                 485                 490

atg cat gat tct aag aac tgg aag aac ctg gtg gtt cca ttt gca aag  1599
```

```
Met His Asp Ser Lys Asn Trp Lys Asn Leu Val Val Pro Phe Ala Lys
                495                 500                 505

gct gtg tgt gaa atg agt aaa caa tct ttg caa gtc cta aag aag tgt  1647
Ala Val Cys Glu Met Ser Lys Gln Ser Leu Gln Val Leu Lys Lys Cys
            510                 515                 520

tgg gca ttt ttg caa gaa tct tct ctg aat ccg ctg atc cag atg ctt  1695
Trp Ala Phe Leu Gln Glu Ser Ser Leu Asn Pro Leu Ile Gln Met Leu
        525                 530                 535

aaa gca gcc atc atc tct cag ctg ctt cat cag act aaa acc gaa cag  1743
Lys Ala Ala Ile Ile Ser Gln Leu Leu His Gln Thr Lys Thr Glu Gln
    540                 545                 550

gat cac tgt aat gtt aaa gct ctt tta gga atg atg aaa gaa ctg cat  1791
Asp His Cys Asn Val Lys Ala Leu Leu Gly Met Met Lys Glu Leu His
555                 560                 565                 570

aag gta aac aaa gct aac tgt cga cta cca gaa aat act ttc aac ata  1839
Lys Val Asn Lys Ala Asn Cys Arg Leu Pro Glu Asn Thr Phe Asn Ile
                575                 580                 585

aat gaa ctc tcc aac tta tta aac ttt tat ata gat aga gga aga cag  1887
Asn Glu Leu Ser Asn Leu Leu Asn Phe Tyr Ile Asp Arg Gly Arg Gln
            590                 595                 600

ctc ttt cgg gat aac cac ctg ata cct gca gaa acc ccc agt cct gtt  1935
Leu Phe Arg Asp Asn His Leu Ile Pro Ala Glu Thr Pro Ser Pro Val
        605                 610                 615

att ttc agt gat ttt cca ttt atc ttt aat tcg cta tcc aaa att aaa  1983
Ile Phe Ser Asp Phe Pro Phe Ile Phe Asn Ser Leu Ser Lys Ile Lys
    620                 625                 630

tta ttg caa gct gat tca cat ata aag atg cag atg tca gaa aag aaa  2031
Leu Leu Gln Ala Asp Ser His Ile Lys Met Gln Met Ser Glu Lys Lys
635                 640                 645                 650

gca tac atg ctt atg cat gaa aca att ctg caa aaa aag gat gaa ttt  2079
Ala Tyr Met Leu Met His Glu Thr Ile Leu Gln Lys Lys Asp Glu Phe
                655                 660                 665

cct cca tca ccc aga ttt ata ctt aga gtc aga cga agt cgc ctg gtt  2127
Pro Pro Ser Pro Arg Phe Ile Leu Arg Val Arg Arg Ser Arg Leu Val
            670                 675                 680

aaa gat gct ctg cgt caa tta agt caa gct gaa gct act gac ttc tgc  2175
Lys Asp Ala Leu Arg Gln Leu Ser Gln Ala Glu Ala Thr Asp Phe Cys
        685                 690                 695

aaa gta tta gtg gtt gaa ttt att aat gaa att tgt cct gag tct gga  2223
Lys Val Leu Val Val Glu Phe Ile Asn Glu Ile Cys Pro Glu Ser Gly
    700                 705                 710

ggg gtt agt tca gag ttc ttc cac tgt atg ttt gaa gag atg acc aag  2271
Gly Val Ser Ser Glu Phe Phe His Cys Met Phe Glu Glu Met Thr Lys
715                 720                 725                 730

cca gaa tat gga atg ttc atg tat cct gaa atg ggt tcc tgc atg tgg  2319
Pro Glu Tyr Gly Met Phe Met Tyr Pro Glu Met Gly Ser Cys Met Trp
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                735                 740                 745

ttt cct gcc aag cct aaa cct gag aag aaa aga tat ttc ctc ttt gga   2367
Phe Pro Ala Lys Pro Lys Pro Glu Lys Lys Arg Tyr Phe Leu Phe Gly
            750                 755                 760

atg ctg tgt gga ctc tcc tta ttc aat tta aat gtt gct aac ctt cct   2415
Met Leu Cys Gly Leu Ser Leu Phe Asn Leu Asn Val Ala Asn Leu Pro
        765                 770                 775

ttc cca ctg gct ctg tat aaa aaa ctt ctg gac caa aag cca tca ttg   2463
Phe Pro Leu Ala Leu Tyr Lys Lys Leu Leu Asp Gln Lys Pro Ser Leu
    780                 785                 790

gaa gat tta aaa gaa ctc agt cct cgg ttg ggg aag agt ttg caa gaa   2511
Glu Asp Leu Lys Glu Leu Ser Pro Arg Leu Gly Lys Ser Leu Gln Glu
795                 800                 805                 810

gtt cta gat gat gct gct gat gac att gga gat gcg ctc tgc ata cgc   2559
Val Leu Asp Asp Ala Ala Asp Asp Ile Gly Asp Ala Leu Cys Ile Arg
                815                 820                 825

ttt tct ata cac tgg gac caa aat gat gtt gac tta att cca aat ggg   2607
Phe Ser Ile His Trp Asp Gln Asn Asp Val Asp Leu Ile Pro Asn Gly
            830                 835                 840

atc tcc ata cct gtg gac caa acc aac aag aga gac tat gtt tct aag   2655
Ile Ser Ile Pro Val Asp Gln Thr Asn Lys Arg Asp Tyr Val Ser Lys
        845                 850                 855

tat att gat tac att ttc aac gtc tct gta aaa gca gtt tat gag gaa   2703
Tyr Ile Asp Tyr Ile Phe Asn Val Ser Val Lys Ala Val Tyr Glu Glu
    860                 865                 870

ttt cag aga gga ttt tat aga gtc tgt gag aag gag ata ctt aga cat   2751
Phe Gln Arg Gly Phe Tyr Arg Val Cys Glu Lys Glu Ile Leu Arg His
875                 880                 885                 890

ttc tac cct gaa gaa cta atg aca gca atc att gga aat act gat tat   2799
Phe Tyr Pro Glu Glu Leu Met Thr Ala Ile Ile Gly Asn Thr Asp Tyr
                895                 900                 905

gac tgg aaa cag ttt gaa cag aat tca aag tat gag caa gga tac caa   2847
Asp Trp Lys Gln Phe Glu Gln Asn Ser Lys Tyr Glu Gln Gly Tyr Gln
            910                 915                 920

aaa tca cat cct act ata cag ttg ttt tgg aag gct ttc cac aaa cta   2895
Lys Ser His Pro Thr Ile Gln Leu Phe Trp Lys Ala Phe His Lys Leu
        925                 930                 935

acc ttg gat gaa aag aaa aaa ttc ctc ttt ttc ctt aca gga cgt gat   2943
Thr Leu Asp Glu Lys Lys Lys Phe Leu Phe Phe Leu Thr Gly Arg Asp
    940                 945                 950

agg ctg cat gca aga ggc ata cag aaa atg gaa ata gta ttt cgc tgt   2991
Arg Leu His Ala Arg Gly Ile Gln Lys Met Glu Ile Val Phe Arg Cys
955                 960                 965                 970

cct gaa act ttc agt gaa aga gat cac cca aca tca ata act tgt cat   3039
Pro Glu Thr Phe Ser Glu Arg Asp His Pro Thr Ser Ile Thr Cys His
                975                 980                 985
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aat att ctc tcc ctc cct aag tat tct aca atg gaa aga atg gag gaa   3087
Asn Ile Leu Ser Leu Pro Lys Tyr Ser Thr Met Glu Arg Met Glu Glu
          990                 995                 1000

gca ctt caa gta gcc atc aac aac aac aga gga ttt gtc tca ccc atg   3135
Ala Leu Gln Val Ala Ile Asn Asn Asn Arg Gly Phe Val Ser Pro Met
        1005                1010                1015

ctc aca cag tca taa tcacctctga gagactcagg gtgggctttc tcacacttgg   3190
Leu Thr Gln Ser  *
    1020

atccttctgt tcttccttac acctaaataa tacaagagat taatgaatag tggttagaag 3250
tagttgaggg agagattggg ggaatgggga gatgatgatg atggtcaaag ggtgcaaaat 3310
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<212> PRT
<213> Homo sapiens

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            20                  25                  30
Arg His Ser Leu Leu Leu Leu Thr Asn His Arg Val Leu Ser Cys Gly
        35                  40                  45
Asp Asn Ser Arg Gly Gln Leu Gly Arg Arg Gly Ala Gln Arg Gly Glu
    50                  55                  60
Leu Pro Glu Pro Ile Gln Ala Leu Glu Thr Leu Ile Val Asp Leu Val
65                  70                  75                  80
Ser Cys Gly Lys Glu His Ser Leu Ala Val Cys His Lys Gly Arg Val
                85                  90                  95
Phe Ala Trp Gly Ala Gly Ser Glu Gly Gln Leu Gly Ile Gly Glu Phe
            100                 105                 110
Lys Glu Ile Ser Phe Thr Pro Lys Lys Ile Met Thr Leu Asn Asp Ile
        115                 120                 125
Lys Ile Ile Gln Val Ser Cys Gly His Tyr His Ser Leu Ala Leu Ser
    130                 135                 140
Lys Asp Ser Gln Val Phe Ser Trp Gly Lys Asn Ser His Gly Gln Leu
145                 150                 155                 160
Gly Leu Gly Lys Glu Phe Pro Ser Gln Ala Ser Pro Gln Arg Val Arg
                165                 170                 175
Ser Leu Glu Gly Ile Pro Leu Ala Gln Val Ala Ala Gly Gly Ala His
            180                 185                 190
Ser Phe Ala Leu Ser Leu Cys Gly Thr Ser Phe Gly Trp Gly Ser Asn
        195                 200                 205
Ser Ala Gly Gln Leu Ala Leu Ser Gly Arg Asn Val Pro Val Gln Ser
    210                 215                 220
Asn Lys Pro Leu Ser Val Gly Ala Leu Lys Asn Leu Gly Val Val Tyr
225                 230                 235                 240
Ile Ser Cys Gly Asp Ala His Thr Ala Val Leu Thr Gln Asp Gly Lys
                245                 250                 255
Val Phe Thr Phe Gly Asp Asn Arg Ser Gly Gln Leu Gly Tyr Ser Pro
            260                 265                 270
Thr Pro Glu Lys Arg Gly Pro Gln Leu Val Glu Arg Ile Asp Gly Leu
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        275                 280                 285
Val Ser Gln Ile Asp Cys Gly Ser Tyr His Thr Leu Ala Tyr Val His
    290                 295                 300
Thr Thr Gly Gln Val Val Ser Phe Gly His Gly Pro Ser Asp Thr Ser
305                 310                 315                 320
Lys Pro Thr His Pro Glu Ala Leu Thr Glu Asn Phe Asp Ile Ser Cys
                325                 330                 335
Leu Ile Ser Ala Glu Asp Phe Val Asp Val Gln Val Lys His Ile Phe
            340                 345                 350
Ala Gly Thr Tyr Ala Asn Phe Val Thr Thr His Gln Asp Thr Ser Ser
        355                 360                 365
Thr Arg Ala Pro Gly Lys Thr Leu Pro Glu Ile Ser Arg Ile Ser Gln
    370                 375                 380
Ser Met Ala Glu Lys Trp Ile Ala Val Lys Arg Arg Ser Thr Glu His
385                 390                 395                 400
Glu Met Ala Lys Ser Glu Ile Arg Met Ile Phe Ser Ser Pro Ala Cys
                405                 410                 415
Leu Thr Ala Ser Phe Leu Lys Lys Arg Gly Thr Gly Glu Thr Thr Ser
            420                 425                 430
Ile Asp Val Asp Leu Glu Met Ala Arg Asp Thr Phe Lys Lys Leu Thr
        435                 440                 445
Lys Lys Glu Trp Ile Ser Ser Met Ile Thr Thr Cys Leu Glu Asp Asp
    450                 455                 460
Leu Leu Arg Ala Leu Pro Cys His Ser Pro His Gln Glu Ala Leu Ser
465                 470                 475                 480
Val Phe Leu Leu Leu Pro Glu Cys Pro Val Met His Asp Ser Lys Asn
                485                 490                 495
Trp Lys Asn Leu Val Val Pro Phe Ala Lys Ala Val Cys Glu Met Ser
            500                 505                 510
Lys Gln Ser Leu Gln Val Leu Lys Lys Cys Trp Ala Phe Leu Gln Glu
        515                 520                 525
Ser Ser Leu Asn Pro Leu Ile Gln Met Leu Lys Ala Ala Ile Ile Ser
    530                 535                 540
Gln Leu Leu His Gln Thr Lys Thr Glu Gln Asp His Cys Asn Val Lys
545                 550                 555                 560
Ala Leu Leu Gly Met Met Lys Glu Leu His Lys Val Asn Lys Ala Asn
                565                 570                 575
Cys Arg Leu Pro Glu Asn Thr Phe Asn Ile Asn Glu Leu Ser Asn Leu
            580                 585                 590
Leu Asn Phe Tyr Ile Asp Arg Gly Arg Gln Leu Phe Arg Asp Asn His
        595                 600                 605
Leu Ile Pro Ala Glu Thr Pro Ser Pro Val Ile Phe Ser Asp Phe Pro
    610                 615                 620
Phe Ile Phe Asn Ser Leu Ser Lys Ile Lys Leu Leu Gln Ala Asp Ser
625                 630                 635                 640
His Ile Lys Met Gln Met Ser Glu Lys Lys Ala Tyr Met Leu Met His
                645                 650                 655
Glu Thr Ile Leu Gln Lys Lys Asp Glu Phe Pro Pro Ser Pro Arg Phe
            660                 665                 670
Ile Leu Arg Val Arg Arg Ser Arg Leu Val Lys Asp Ala Leu Arg Gln
        675                 680                 685
Leu Ser Gln Ala Glu Ala Thr Asp Phe Cys Lys Val Leu Val Val Glu
    690                 695                 700
Phe Ile Asn Glu Ile Cys Pro Glu Ser Gly Gly Val Ser Ser Glu Phe
705                 710                 715                 720
Phe His Cys Met Phe Glu Glu Met Thr Lys Pro Glu Tyr Gly Met Phe
                725                 730                 735
Met Tyr Pro Glu Met Gly Ser Cys Met Trp Phe Pro Ala Lys Pro Lys
            740                 745                 750
Pro Glu Lys Lys Arg Tyr Phe Leu Phe Gly Met Leu Cys Gly Leu Ser
        755                 760                 765
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Leu Phe Asn Leu Asn Val Ala Asn Leu Pro Phe Pro Leu Ala Leu Tyr
    770                 775                 780
Lys Lys Leu Leu Asp Gln Lys Pro Ser Leu Glu Asp Leu Lys Glu Leu
785                 790                 795                 800
Ser Pro Arg Leu Gly Lys Ser Leu Gln Glu Val Leu Asp Asp Ala Ala
                805                 810                 815
Asp Asp Ile Gly Asp Ala Leu Cys Ile Arg Phe Ser Ile His Trp Asp
            820                 825                 830
Gln Asn Asp Val Asp Leu Ile Pro Asn Gly Ile Ser Ile Pro Val Asp
        835                 840                 845
Gln Thr Asn Lys Arg Asp Tyr Val Ser Lys Tyr Ile Asp Tyr Ile Phe
    850                 855                 860
Asn Val Ser Val Lys Ala Val Tyr Glu Glu Phe Gln Arg Gly Phe Tyr
865                 870                 875                 880
Arg Val Cys Glu Lys Glu Ile Leu Arg His Phe Tyr Pro Glu Glu Leu
                885                 890                 895
Met Thr Ala Ile Ile Gly Asn Thr Asp Tyr Asp Trp Lys Gln Phe Glu
            900                 905                 910
Gln Asn Ser Lys Tyr Glu Gln Gly Tyr Gln Lys Ser His Pro Thr Ile
        915                 920                 925
Gln Leu Phe Trp Lys Ala Phe His Lys Leu Thr Leu Asp Glu Lys Lys
    930                 935                 940
Lys Phe Leu Phe Phe Leu Thr Gly Arg Asp Arg Leu His Ala Arg Gly
945                 950                 955                 960
Ile Gln Lys Met Glu Ile Val Phe Arg Cys Pro Glu Thr Phe Ser Glu
                965                 970                 975
Arg Asp His Pro Thr Ser Ile Thr Cys His Asn Ile Leu Ser Leu Pro
            980                 985                 990
Lys Tyr Ser Thr Met Glu Arg Met Glu Glu Ala Leu Gln Val Ala Ile
        995                 1000                1005
Asn Asn Asn Arg Gly Phe Val Ser Pro Met Leu Thr Gln Ser
    1010                1015                1020
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gggcgctccc tgcagggctc tgcgcggcgt gccgcggcgg ccgcgggctc cggccccggg 120
ccatgagccc ctccgcgact cggcgctgag cccgccaccg gtccagcgcc ccaggacccg 180
ccgccggctg ccggcttgcc gaagcccccc caggatcccc tcaacaagg atg gaa ctg 238
                                                    Met Glu Leu
                                                     1

aag gcc gag gag gag gag gtg ggt ggc gtc cag ccg gtg agc atc cag   286
Lys Ala Glu Glu Glu Glu Val Gly Gly Val Gln Pro Val Ser Ile Gln
 5                  10                  15

gcc ttc gcc agc agc tcc aca ctg cac ggc ctg gcc cac atc ttc tcc   334
Ala Phe Ala Ser Ser Ser Thr Leu His Gly Leu Ala His Ile Phe Ser
 20                  25                  30                  35

tac gag cgg ctg tct ctg aag cgg gca ctg tgg gcc ctg tgc ttc ctg   382
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Tyr Glu Arg Leu Ser Leu Lys Arg Ala Leu Trp Ala Leu Cys Phe Leu
                40                  45                  50

ggc tcg ctg gct gtg ctg ctg tgt gtg tgc acg gag cgt gtg cag tac   430
Gly Ser Leu Ala Val Leu Leu Cys Val Cys Thr Glu Arg Val Gln Tyr
            55                  60                  65

tac ttc cac tac cac cat gtc acc aag ctc gac gag gtg gct gcc tct   478
Tyr Phe His Tyr His His Val Thr Lys Leu Asp Glu Val Ala Ala Ser
        70                  75                  80

cag ctt acc ttc cct gct gtc acg ctg tgc aac ctc aac gag ttc cgc   526
Gln Leu Thr Phe Pro Ala Val Thr Leu Cys Asn Leu Asn Glu Phe Arg
    85                  90                  95

ttt agc caa gtc tcc aag aat gac ctg tat cat gct ggg gag ctg ctg   574
Phe Ser Gln Val Ser Lys Asn Asp Leu Tyr His Ala Gly Glu Leu Leu
100                 105                 110                 115

gcc ctg ctc aac aac agg tat gag ata cca gac aca cag atg gca gat   622
Ala Leu Leu Asn Asn Arg Tyr Glu Ile Pro Asp Thr Gln Met Ala Asp
                120                 125                 130

gaa aag cag ctg gag ata ctg cag gac aaa gcc aac ttc cgc agc ttc   670
Glu Lys Gln Leu Glu Ile Leu Gln Asp Lys Ala Asn Phe Arg Ser Phe
            135                 140                 145

aaa ccc aaa ccc ttc aac atg cgt gag ttc tac gac cga gct ggg cac   718
Lys Pro Lys Pro Phe Asn Met Arg Glu Phe Tyr Asp Arg Ala Gly His
        150                 155                 160

gac att cga gac atg ctg ctc tcc tgc cac ttc cgg ggg gag gtc tgc   766
Asp Ile Arg Asp Met Leu Leu Ser Cys His Phe Arg Gly Glu Val Cys
    165                 170                 175

agc gct gaa gac ttc aag gtg gtc ttc aca cgc tat gga aag tgc tac   814
Ser Ala Glu Asp Phe Lys Val Val Phe Thr Arg Tyr Gly Lys Cys Tyr
180                 185                 190                 195

acg ttc aac tcg ggc cga gat ggg cgg ccg cgg ctg aag acc atg aag   862
Thr Phe Asn Ser Gly Arg Asp Gly Arg Pro Arg Leu Lys Thr Met Lys
                200                 205                 210

gat ggg acg ggc aat ggg ctg gaa atc atg ctg gac atc cag cag gac   910
Asp Gly Thr Gly Asn Gly Leu Glu Ile Met Leu Asp Ile Gln Gln Asp
            215                 220                 225

gag tac ctg cct gtg tgg ggg gag act gac gag acg tcc ttc gaa gca   958
Glu Tyr Leu Pro Val Trp Gly Glu Thr Asp Glu Thr Ser Phe Glu Ala
        230                 235                 240

ggc atc aaa gtg cag atc cat agt cag gat gaa cct cct ttc atc gac   1006
Gly Ile Lys Val Gln Ile His Ser Gln Asp Glu Pro Pro Phe Ile Asp
    245                 250                 255

cag ctg ggc ttt ggc gtg gcc cca ggc ttc cag acc ttt gtg gcc tgc   1054
Gln Leu Gly Phe Gly Val Ala Pro Gly Phe Gln Thr Phe Val Ala Cys
260                 265                 270                 275

cag gag cag cgg ctc atc tac ctg ccc cca ccc tgg ggc acc tgc aaa   1102
Gln Glu Gln Arg Leu Ile Tyr Leu Pro Pro Pro Trp Gly Thr Cys Lys
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                280                 285                 290

gct gtt acc atg gac tcg gat ttg gat ttc ttc gac tcc tac agc atc   1150
Ala Val Thr Met Asp Ser Asp Leu Asp Phe Phe Asp Ser Tyr Ser Ile
            295                 300                 305

act gcc tgc cgc atc gac tgt gag acg cgc tac ctg gtg gag aac tgc   1198
Thr Ala Cys Arg Ile Asp Cys Glu Thr Arg Tyr Leu Val Glu Asn Cys
        310                 315                 320

aac tgc cgc atg gtg cac atg cca ggg gat gcc cca tac tgt act cca   1246
Asn Cys Arg Met Val His Met Pro Gly Asp Ala Pro Tyr Cys Thr Pro
    325                 330                 335

gag cag tac aag gag tgt gca gat cct gct ctg gac ttc ctg gtg gag   1294
Glu Gln Tyr Lys Glu Cys Ala Asp Pro Ala Leu Asp Phe Leu Val Glu
340                 345                 350                 355

aag gac cag gag tac tgc gtg tgt gaa atg cct tgc aac ctg acc cgc   1342
Lys Asp Gln Glu Tyr Cys Val Cys Glu Met Pro Cys Asn Leu Thr Arg
                360                 365                 370

tat ggc aaa gag ctg tcc atg gtc aag atc ccc agc aaa gcc tca gcc   1390
Tyr Gly Lys Glu Leu Ser Met Val Lys Ile Pro Ser Lys Ala Ser Ala
            375                 380                 385

aag tac ctg gcc aag aag ttc aac aaa tct gag caa tac ata ggg gag   1438
Lys Tyr Leu Ala Lys Lys Phe Asn Lys Ser Glu Gln Tyr Ile Gly Glu
        390                 395                 400

aac atc ctg gtg ctg gac att ttc ttt gaa gtc ctc aac tat gag acc   1486
Asn Ile Leu Val Leu Asp Ile Phe Phe Glu Val Leu Asn Tyr Glu Thr
    405                 410                 415

att gaa cag aag aag gcc tat gag att gca ggg ctc ctg ggt gag ctg   1534
Ile Glu Gln Lys Lys Ala Tyr Glu Ile Ala Gly Leu Leu Gly Glu Leu
420                 425                 430                 435

ctg atg aca cct gtc ccc ttc tca tgc cat ggg cat ggc gtg gct ccc   1582
Leu Met Thr Pro Val Pro Phe Ser Cys His Gly His Gly Val Ala Pro
                440                 445                 450

tat cat cca aaa gca ggg tgc tca ctt ctg tcc cat gag ggt cct cca   1630
Tyr His Pro Lys Ala Gly Cys Ser Leu Leu Ser His Glu Gly Pro Pro
            455                 460                 465

ccc cag agg ccc ttc ccc aaa ccc tgt tgt ctt ggt gac atc ggg ggc   1678
Pro Gln Arg Pro Phe Pro Lys Pro Cys Cys Leu Gly Asp Ile Gly Gly
        470                 475                 480

cag atg ggg ctg ttc atc ggg gcc agc atc ctc acg gtg ctg gag ctc   1726
Gln Met Gly Leu Phe Ile Gly Ala Ser Ile Leu Thr Val Leu Glu Leu
    485                 490                 495

ttt gac tac gcc tac gag gtc att aag cac aag ctg tgc cga cga gga   1774
Phe Asp Tyr Ala Tyr Glu Val Ile Lys His Lys Leu Cys Arg Arg Gly
500                 505                 510                 515

aaa tgc cag aag gag gcc aaa agg agc agt gcg gac aag ggc gtg gcc   1822
Lys Cys Gln Lys Glu Ala Lys Arg Ser Ser Ala Asp Lys Gly Val Ala
                520                 525                 530
```

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ctc agc ctg gac gac gtc aaa aga cac aac ccg tgc gag agc ctt cgg   1870
Leu Ser Leu Asp Asp Val Lys Arg His Asn Pro Cys Glu Ser Leu Arg
            535                 540                 545

ggc cac cct gcc ggg atg aca tac gct gcc aac atc cta cct cac cat   1918
Gly His Pro Ala Gly Met Thr Tyr Ala Ala Asn Ile Leu Pro His His
        550                 555                 560

ccg gcc cga ggc acg ttc gag gac ttt acc tgc tga gccccgcagg        1964
Pro Ala Arg Gly Thr Phe Glu Asp Phe Thr Cys  *
    565                 570

ccgctgaacc aaaggcctag atggggagga ctaggagagc grgggggccc ccagctgcct 2024
cctcacatct gccctgggra ctccccacac tccggggcag atctttcctc ttgtctgtgg 2084
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<212> PRT
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<400> 18

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Ser Ile Gln Ala Phe Ala Ser Ser Ser Thr Leu His Gly Leu Ala His
            20                  25                  30
Ile Phe Ser Tyr Glu Arg Leu Ser Leu Lys Arg Ala Leu Trp Ala Leu
        35                  40                  45
Cys Phe Leu Gly Ser Leu Ala Val Leu Leu Cys Val Cys Thr Glu Arg
    50                  55                  60
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Val Gln Tyr Tyr Phe His Tyr His His Val Thr Lys Leu Asp Glu Val
65                  70                  75                  80
Ala Ala Ser Gln Leu Thr Phe Pro Ala Val Thr Leu Cys Asn Leu Asn
                85                  90                  95
Glu Phe Arg Phe Ser Gln Val Ser Lys Asn Asp Leu Tyr His Ala Gly
            100                 105                 110
Glu Leu Leu Ala Leu Leu Asn Asn Arg Tyr Glu Ile Pro Asp Thr Gln
        115                 120                 125
Met Ala Asp Glu Lys Gln Leu Glu Ile Leu Gln Asp Lys Ala Asn Phe
    130                 135                 140
Arg Ser Phe Lys Pro Lys Pro Phe Asn Met Arg Glu Phe Tyr Asp Arg
145                 150                 155                 160
Ala Gly His Asp Ile Arg Asp Met Leu Leu Ser Cys His Phe Arg Gly
                165                 170                 175
Glu Val Cys Ser Ala Glu Asp Phe Lys Val Val Phe Thr Arg Tyr Gly
            180                 185                 190
Lys Cys Tyr Thr Phe Asn Ser Gly Arg Asp Gly Arg Pro Arg Leu Lys
        195                 200                 205
Thr Met Lys Asp Gly Thr Gly Asn Gly Leu Glu Ile Met Leu Asp Ile
    210                 215                 220
Gln Gln Asp Glu Tyr Leu Pro Val Trp Gly Glu Thr Asp Glu Thr Ser
225                 230                 235                 240
Phe Glu Ala Gly Ile Lys Val Gln Ile His Ser Gln Asp Glu Pro Pro
                245                 250                 255
Phe Ile Asp Gln Leu Gly Phe Gly Val Ala Pro Gly Phe Gln Thr Phe
            260                 265                 270
Val Ala Cys Gln Glu Gln Arg Leu Ile Tyr Leu Pro Pro Pro Trp Gly
        275                 280                 285
Thr Cys Lys Ala Val Thr Met Asp Ser Asp Leu Asp Phe Phe Asp Ser
    290                 295                 300
Tyr Ser Ile Thr Ala Cys Arg Ile Asp Cys Glu Thr Arg Tyr Leu Val
305                 310                 315                 320
Glu Asn Cys Asn Cys Arg Met Val His Met Pro Gly Asp Ala Pro Tyr
                325                 330                 335
Cys Thr Pro Glu Gln Tyr Lys Glu Cys Ala Asp Pro Ala Leu Asp Phe
            340                 345                 350
Leu Val Glu Lys Asp Gln Glu Tyr Cys Val Cys Glu Met Pro Cys Asn
        355                 360                 365
Leu Thr Arg Tyr Gly Lys Glu Leu Ser Met Val Lys Ile Pro Ser Lys
    370                 375                 380
Ala Ser Ala Lys Tyr Leu Ala Lys Lys Phe Asn Lys Ser Glu Gln Tyr
385                 390                 395                 400
Ile Gly Glu Asn Ile Leu Val Leu Asp Ile Phe Phe Glu Val Leu Asn
                405                 410                 415
Tyr Glu Thr Ile Glu Gln Lys Lys Ala Tyr Glu Ile Ala Gly Leu Leu
            420                 425                 430
Gly Glu Leu Leu Met Thr Pro Val Pro Phe Ser Cys His Gly His Gly
        435                 440                 445
Val Ala Pro Tyr His Pro Lys Ala Gly Cys Ser Leu Leu Ser His Glu
    450                 455                 460
Gly Pro Pro Pro Gln Arg Pro Phe Pro Lys Pro Cys Cys Leu Gly Asp
465                 470                 475                 480
Ile Gly Gly Gln Met Gly Leu Phe Ile Gly Ala Ser Ile Leu Thr Val
                485                 490                 495
Leu Glu Leu Phe Asp Tyr Ala Tyr Glu Val Ile Lys His Lys Leu Cys
            500                 505                 510
Arg Arg Gly Lys Cys Gln Lys Glu Ala Lys Arg Ser Ser Ala Asp Lys
        515                 520                 525
Gly Val Ala Leu Ser Leu Asp Asp Val Lys Arg His Asn Pro Cys Glu
    530                 535                 540
Ser Leu Arg Gly His Pro Ala Gly Met Thr Tyr Ala Ala Asn Ile Leu
```

```
545                 550                 555                 560
Pro His His Pro Ala Arg Gly Thr Phe Glu Asp Phe Thr Cys
                565                 570
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<210> 19
<211> 1373
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (31)...(1373)

<400> 19

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gaattysggk tcrmmcmcgs stccscagca atg tct cca cca ctg ctg ctg cta  54
                                Met Ser Pro Pro Leu Leu Leu Leu
                                 1               5

ccc ttg ctg ctg ctg ctg cct ctg ctg aat gtg gag cct gct ggg gcc  102
Pro Leu Leu Leu Leu Leu Pro Leu Leu Asn Val Glu Pro Ala Gly Ala
     10                  15                  20

aca ctg atc cgg atc cct ctt cgt caa gtc cac cct gga cgc agg acc  150
Thr Leu Ile Arg Ile Pro Leu Arg Gln Val His Pro Gly Arg Arg Thr
 25                  30                  35                  40

ctg aac cta ctg agg gga tgg gga aaa cca gca gag ctc ccc aag ttg  198
Leu Asn Leu Leu Arg Gly Trp Gly Lys Pro Ala Glu Leu Pro Lys Leu
                 45                  50                  55

ggg gcc cca tcc cct ggg gac aag cct gcc tcg gta cct ctc tcc aaa  246
Gly Ala Pro Ser Pro Gly Asp Lys Pro Ala Ser Val Pro Leu Ser Lys
             60                  65                  70

ttc ctg gat gcc cag tat ttt ggg gaa att ggg ctg gga acg cct cca  294
Phe Leu Asp Ala Gln Tyr Phe Gly Glu Ile Gly Leu Gly Thr Pro Pro
         75                  80                  85

caa aac ttc act gtt gcc ttt gac act ggc tcc tcc aat ctc tgg gtc  342
Gln Asn Phe Thr Val Ala Phe Asp Thr Gly Ser Ser Asn Leu Trp Val
     90                  95                  100

ccg tcc agg aga tgc cac ttc ttc agt gtg ccc tgc tgg ttc cac cac  390
Pro Ser Arg Arg Cys His Phe Phe Ser Val Pro Cys Trp Phe His His
105                 110                 115                 120

cgc ttc aat ccc aat gcc tcc agc tcc ttc aag ccc agt ggg acc aag  438
Arg Phe Asn Pro Asn Ala Ser Ser Ser Phe Lys Pro Ser Gly Thr Lys
                125                 130                 135

ttt gcc att cag tat gga act ggg cgg gta gat gga atc ctg agt gag  486
Phe Ala Ile Gln Tyr Gly Thr Gly Arg Val Asp Gly Ile Leu Ser Glu
            140                 145                 150

gac aag ctg act att ggt gga atc aag ggt gca tcc gtg att ttc ggg  534
Asp Lys Leu Thr Ile Gly Gly Ile Lys Gly Ala Ser Val Ile Phe Gly
        155                 160                 165

gaa gct ctg tgg gaa tcc agc ctg gtc ttc act gtt tcc cgc ccc gat  582
Glu Ala Leu Trp Glu Ser Ser Leu Val Phe Thr Val Ser Arg Pro Asp
```

```
    170                 175                 180

ggg ata ttg ggc ctc ggt ttt ccc att ctg tct gtg gaa gga gtt cgg   630
Gly Ile Leu Gly Leu Gly Phe Pro Ile Leu Ser Val Glu Gly Val Arg
185                 190                 195                 200

ccc ccg ctg gat gta ctg gtg gag cag ggg cta ttg gat aag cct gtc   678
Pro Pro Leu Asp Val Leu Val Glu Gln Gly Leu Leu Asp Lys Pro Val
                205                 210                 215

ttc tcc ttt tac ttc aac agg gac cct gaa gtg gct gat gga gga gag   726
Phe Ser Phe Tyr Phe Asn Arg Asp Pro Glu Val Ala Asp Gly Gly Glu
            220                 225                 230

ctg gtc ctg ggg ggc tca gac ccg gca cac tac atc cca ccc ctc acc   774
Leu Val Leu Gly Gly Ser Asp Pro Ala His Tyr Ile Pro Pro Leu Thr
        235                 240                 245

ttc gtg cca gtc aca gtc ccc gcc tac tgg cag atc cac atg gag cgt   822
Phe Val Pro Val Thr Val Pro Ala Tyr Trp Gln Ile His Met Glu Arg
    250                 255                 260

gtg aag gtg ggc tca cgg ctg act ctc tgt gcc cag ggc tgt gct gcc   870
Val Lys Val Gly Ser Arg Leu Thr Leu Cys Ala Gln Gly Cys Ala Ala
265                 270                 275                 280

atc ctg gat aca ggc aca cct gtc atc gta gga ccc act gag gag atc   918
Ile Leu Asp Thr Gly Thr Pro Val Ile Val Gly Pro Thr Glu Glu Ile
                285                 290                 295

cgg gcc ctg cat gca gcc att ggg gga atc ccc ttg ctg gct ggg gag   966
Arg Ala Leu His Ala Ala Ile Gly Gly Ile Pro Leu Leu Ala Gly Glu
            300                 305                 310

tac atc atc cgg tgc tca gaa atc cca aag ctc ccc gca gtc tca ctc   1014
Tyr Ile Ile Arg Cys Ser Glu Ile Pro Lys Leu Pro Ala Val Ser Leu
        315                 320                 325

ctc att ggg ggg gtc tgg ttt aat ctc acg gcc cag gat tac gtc atc   1062
Leu Ile Gly Gly Val Trp Phe Asn Leu Thr Ala Gln Asp Tyr Val Ile
    330                 335                 340

cag ttt gct cag ggt gac gtc cgc ctc tgc ttg tcc ggc ttc cgg gcc   1110
Gln Phe Ala Gln Gly Asp Val Arg Leu Cys Leu Ser Gly Phe Arg Ala
345                 350                 355                 360

ttg gac atc gct tcg cct cca gta cct gtg tgg atc ctc ggc gac gtt   1158
Leu Asp Ile Ala Ser Pro Pro Val Pro Val Trp Ile Leu Gly Asp Val
                365                 370                 375

ttc ttg ggg gcg tat gtg acc gtc ttc gac cgc ggg gac atg aag agc   1206
Phe Leu Gly Ala Tyr Val Thr Val Phe Asp Arg Gly Asp Met Lys Ser
            380                 385                 390

ggc gca cga gtg gga ctg gcg cgc gct cgc cct cgc gga gcg gac ctg   1254
Gly Ala Arg Val Gly Leu Ala Arg Ala Arg Pro Arg Gly Ala Asp Leu
        395                 400                 405

gga agg cgc gag acc gcg cag gcg cag tac cgc ggg tgc cgc cca ggt   1302
Gly Arg Arg Glu Thr Ala Gln Ala Gln Tyr Arg Gly Cys Arg Pro Gly
    410                 415                 420
```

```
gat gcg cat gcg cac cgg gta gca gag cta gcg cta ctc agt aaa aat   1350
Asp Ala His Ala His Arg Val Ala Glu Leu Ala Leu Leu Ser Lys Asn
425                 430                 435                 440

cca ata ttt cca ttg aaa aaa aa                                   1373
Pro Ile Phe Pro Leu Lys Lys
                445
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<210> 20
<211> 448
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (448)...(448)
<223> Xaa = Any Amino Acid

<400> 20

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Met Ser Pro Pro Leu Leu Leu Leu Pro Leu Leu Leu Leu Leu Pro Leu
 1               5                  10                  15
Leu Asn Val Glu Pro Ala Gly Ala Thr Leu Ile Arg Ile Pro Leu Arg
            20                  25                  30
Gln Val His Pro Gly Arg Arg Thr Leu Asn Leu Leu Arg Gly Trp Gly
        35                  40                  45
Lys Pro Ala Glu Leu Pro Lys Leu Gly Ala Pro Ser Pro Gly Asp Lys
    50                  55                  60
Pro Ala Ser Val Pro Leu Ser Lys Phe Leu Asp Ala Gln Tyr Phe Gly
65                  70                  75                  80
Glu Ile Gly Leu Gly Thr Pro Pro Gln Asn Phe Thr Val Ala Phe Asp
                85                  90                  95
Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Arg Arg Cys His Phe Phe
            100                 105                 110
Ser Val Pro Cys Trp Phe His His Arg Phe Asn Pro Asn Ala Ser Ser
        115                 120                 125
Ser Phe Lys Pro Ser Gly Thr Lys Phe Ala Ile Gln Tyr Gly Thr Gly
    130                 135                 140
Arg Val Asp Gly Ile Leu Ser Glu Asp Lys Leu Thr Ile Gly Gly Ile
145                 150                 155                 160
Lys Gly Ala Ser Val Ile Phe Gly Glu Ala Leu Trp Glu Ser Ser Leu
                165                 170                 175
Val Phe Thr Val Ser Arg Pro Asp Gly Ile Leu Gly Leu Gly Phe Pro
            180                 185                 190
Ile Leu Ser Val Glu Gly Val Arg Pro Pro Leu Asp Val Leu Val Glu
        195                 200                 205
Gln Gly Leu Leu Asp Lys Pro Val Phe Ser Phe Tyr Phe Asn Arg Asp
    210                 215                 220
Pro Glu Val Ala Asp Gly Gly Glu Leu Val Leu Gly Gly Ser Asp Pro
225                 230                 235                 240
Ala His Tyr Ile Pro Pro Leu Thr Phe Val Pro Val Thr Val Pro Ala
                245                 250                 255
Tyr Trp Gln Ile His Met Glu Arg Val Lys Val Gly Ser Arg Leu Thr
            260                 265                 270
Leu Cys Ala Gln Gly Cys Ala Ala Ile Leu Asp Thr Gly Thr Pro Val
        275                 280                 285
Ile Val Gly Pro Thr Glu Glu Ile Arg Ala Leu His Ala Ala Ile Gly
    290                 295                 300
Gly Ile Pro Leu Leu Ala Gly Glu Tyr Ile Ile Arg Cys Ser Glu Ile
305                 310                 315                 320
```

```
Pro Lys Leu Pro Ala Val Ser Leu Leu Ile Gly Gly Val Trp Phe Asn
                325                 330                 335
Leu Thr Ala Gln Asp Tyr Val Ile Gln Phe Ala Gln Gly Asp Val Arg
            340                 345                 350
Leu Cys Leu Ser Gly Phe Arg Ala Leu Asp Ile Ala Ser Pro Pro Val
        355                 360                 365
Pro Val Trp Ile Leu Gly Asp Val Phe Leu Gly Ala Tyr Val Thr Val
    370                 375                 380
Phe Asp Arg Gly Asp Met Lys Ser Gly Ala Arg Val Gly Leu Ala Arg
385                 390                 395                 400
Ala Arg Pro Arg Gly Ala Asp Leu Gly Arg Arg Glu Thr Ala Gln Ala
                405                 410                 415
Gln Tyr Arg Gly Cys Arg Pro Gly Asp Ala His Ala His Arg Val Ala
            420                 425                 430
Glu Leu Ala Leu Leu Ser Lys Asn Pro Ile Phe Pro Leu Lys Lys Xaa
        435                 440                 445


<210> 21
<211> 1506
<212> DNA
<213> Homo sapiens


<220>
<221> CDS
<222> (1)...(1506)

<400> 21
atg tca tcc tca ggc acg cca gac tta cct gtc cta ctc acc gat ttg   48
Met Ser Ser Ser Gly Thr Pro Asp Leu Pro Val Leu Leu Thr Asp Leu
 1               5                  10                  15

aag att caa tat act aag atc ttc ata aac aat gaa tgg cat gat tca   96
Lys Ile Gln Tyr Thr Lys Ile Phe Ile Asn Asn Glu Trp His Asp Ser
            20                  25                  30

gtg agt ggc aag aaa ttt cct gtc ttt aat cct gca act gag gag gag   144
Val Ser Gly Lys Lys Phe Pro Val Phe Asn Pro Ala Thr Glu Glu Glu
        35                  40                  45

ctc tgc cag gta gaa gaa gga gat aag gag gat gtt gac aag gca gtg   192
Leu Cys Gln Val Glu Glu Gly Asp Lys Glu Asp Val Asp Lys Ala Val
    50                  55                  60

aag gcc gca aga cag gct ttt cag att gga tct ccg tgg cgt act atg   240
Lys Ala Ala Arg Gln Ala Phe Gln Ile Gly Ser Pro Trp Arg Thr Met
65                  70                  75                  80

gat gct tcc gag agg ggg cga cta tta tac aag ttg gct gat tta atc   288
Asp Ala Ser Glu Arg Gly Arg Leu Leu Tyr Lys Leu Ala Asp Leu Ile
                85                  90                  95

gaa aga gat cgt ctg ctg ctg gcg aca atg gag tca atg aat ggt gga   336
Glu Arg Asp Arg Leu Leu Leu Ala Thr Met Glu Ser Met Asn Gly Gly
            100                 105                 110

aaa ctc tat tcc aat gca tat ctg agt gat tta gca ggc tgc atc aaa   384
Lys Leu Tyr Ser Asn Ala Tyr Leu Ser Asp Leu Ala Gly Cys Ile Lys
        115                 120                 125
```

```
aca ttg cgc tac tgt gca ggt tgg gct gac aag atc cag ggc cgt aca   432
Thr Leu Arg Tyr Cys Ala Gly Trp Ala Asp Lys Ile Gln Gly Arg Thr
    130                 135                 140

ata cca att gat gga aat ttt ttt aca tat aca aga cat gaa cct att   480
Ile Pro Ile Asp Gly Asn Phe Phe Thr Tyr Thr Arg His Glu Pro Ile
145                 150                 155                 160

ggt gta tgt ggc caa atc att cct tgg aat ttc ccg ttg gtt atg ctc   528
Gly Val Cys Gly Gln Ile Ile Pro Trp Asn Phe Pro Leu Val Met Leu
                165                 170                 175

att tgg aag ata ggg cct gca ctg agc tgt gga aac aca gtg gtt gtc   576
Ile Trp Lys Ile Gly Pro Ala Leu Ser Cys Gly Asn Thr Val Val Val
            180                 185                 190

aaa cca gca gag caa act cct ctc act gct ctc cac gtg gca tct tta   624
Lys Pro Ala Glu Gln Thr Pro Leu Thr Ala Leu His Val Ala Ser Leu
        195                 200                 205

ata aaa gag gca ggg ttt cct cct gga gta gtg aat att gtt cct ggt   672
Ile Lys Glu Ala Gly Phe Pro Pro Gly Val Val Asn Ile Val Pro Gly
    210                 215                 220

tat ggg cct aca gca ggg gca gcc att tct tct cac atg gat ata gac   720
Tyr Gly Pro Thr Ala Gly Ala Ala Ile Ser Ser His Met Asp Ile Asp
225                 230                 235                 240

aaa gta gcc ttc aca gga tca aca gag gtt ggc aag ttg atc aaa gaa   768
Lys Val Ala Phe Thr Gly Ser Thr Glu Val Gly Lys Leu Ile Lys Glu
                245                 250                 255

gct gcc ggg aaa agc aat ctg aag agg gtg acc ctg gag ctt gga gga   816
Ala Ala Gly Lys Ser Asn Leu Lys Arg Val Thr Leu Glu Leu Gly Gly
            260                 265                 270

aag agc cct tgc att gtg tta gct gat gcc gac ttg gac aat gct gtt   864
Lys Ser Pro Cys Ile Val Leu Ala Asp Ala Asp Leu Asp Asn Ala Val
        275                 280                 285

gaa ttt gca cac cat ggg gta ttc tac cac cag ggc cag tgt tgt ata   912
Glu Phe Ala His His Gly Val Phe Tyr His Gln Gly Gln Cys Cys Ile
    290                 295                 300

gcc gca tcc agg att ttt gtg gaa gaa tca att tat gat gag ttt gtt   960
Ala Ala Ser Arg Ile Phe Val Glu Glu Ser Ile Tyr Asp Glu Phe Val
305                 310                 315                 320

cga agg agt gtt gag cgg gct aag aag tat atc ctt gga aat cct ctg  1008
Arg Arg Ser Val Glu Arg Ala Lys Lys Tyr Ile Leu Gly Asn Pro Leu
                325                 330                 335

acc cca gga gtc act caa ggc cct cag att gac aag gaa caa tat gat  1056
Thr Pro Gly Val Thr Gln Gly Pro Gln Ile Asp Lys Glu Gln Tyr Asp
            340                 345                 350

aaa ata ctt gac ctc att gag agt ggg aag aaa gaa ggg gcc aaa ctg  1104
Lys Ile Leu Asp Leu Ile Glu Ser Gly Lys Lys Glu Gly Ala Lys Leu
        355                 360                 365

gaa tgt gga gga ggc ccg tgg ggg aat aaa ggc tac ttt gtc cag ccc  1152
```

```
Glu Cys Gly Gly Gly Pro Trp Gly Asn Lys Gly Tyr Phe Val Gln Pro
    370                 375                 380

aca gtg ttc tct aat gtt aca gat gag atg cgc att gcc aaa gag gag   1200
Thr Val Phe Ser Asn Val Thr Asp Glu Met Arg Ile Ala Lys Glu Glu
385                 390                 395                 400

att ttt gga cca gtg cag caa atc atg aag ttt aaa tct tta gat gac   1248
Ile Phe Gly Pro Val Gln Gln Ile Met Lys Phe Lys Ser Leu Asp Asp
                405                 410                 415

gtg atc aaa aga gca aac aat act ttc tat ggc tta tca gca gga gtg   1296
Val Ile Lys Arg Ala Asn Asn Thr Phe Tyr Gly Leu Ser Ala Gly Val
            420                 425                 430

ttt acc aaa gac att gat aaa gcc ata aca atc tcc tct gct ctg cag   1344
Phe Thr Lys Asp Ile Asp Lys Ala Ile Thr Ile Ser Ser Ala Leu Gln
        435                 440                 445

gca gga aca gtg tgg gtg aat tgc tat ggc gtg gta agt gcc cag tgc   1392
Ala Gly Thr Val Trp Val Asn Cys Tyr Gly Val Val Ser Ala Gln Cys
    450                 455                 460

ccc ttt ggc gga ttc aag atg tct gga aat gga aga gaa ctg gga gag   1440
Pro Phe Gly Gly Phe Lys Met Ser Gly Asn Gly Arg Glu Leu Gly Glu
465                 470                 475                 480

tac ggt ttc cat gaa tat aca gag gtc aaa aca gtc aca gtg aaa atc   1488
Tyr Gly Phe His Glu Tyr Thr Glu Val Lys Thr Val Thr Val Lys Ile
                485                 490                 495

tct cag aag aac tca taa                                          1506
Ser Gln Lys Asn Ser  *
            500
```

<210> 22
<211> 501
<212> PRT
<213> Homo sapiens

<400> 22

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Met Ser Ser Ser Gly Thr Pro Asp Leu Pro Val Leu Leu Thr Asp Leu
 1               5                  10                  15
Lys Ile Gln Tyr Thr Lys Ile Phe Ile Asn Asn Glu Trp His Asp Ser
            20                  25                  30
Val Ser Gly Lys Lys Phe Pro Val Phe Asn Pro Ala Thr Glu Glu Glu
        35                  40                  45
Leu Cys Gln Val Glu Glu Gly Asp Lys Glu Asp Val Asp Lys Ala Val
    50                  55                  60
Lys Ala Ala Arg Gln Ala Phe Gln Ile Gly Ser Pro Trp Arg Thr Met
65                  70                  75                  80
Asp Ala Ser Glu Arg Gly Arg Leu Leu Tyr Lys Leu Ala Asp Leu Ile
                85                  90                  95
Glu Arg Asp Arg Leu Leu Leu Ala Thr Met Glu Ser Met Asn Gly Gly
            100                 105                 110
Lys Leu Tyr Ser Asn Ala Tyr Leu Ser Asp Leu Ala Gly Cys Ile Lys
        115                 120                 125
Thr Leu Arg Tyr Cys Ala Gly Trp Ala Asp Lys Ile Gln Gly Arg Thr
    130                 135                 140
Ile Pro Ile Asp Gly Asn Phe Phe Thr Tyr Thr Arg His Glu Pro Ile
```

```
145                 150                 155                 160
Gly Val Cys Gly Gln Ile Ile Pro Trp Asn Phe Pro Leu Val Met Leu
                165                 170                 175
Ile Trp Lys Ile Gly Pro Ala Leu Ser Cys Gly Asn Thr Val Val Val
            180                 185                 190
Lys Pro Ala Glu Gln Thr Pro Leu Thr Ala Leu His Val Ala Ser Leu
        195                 200                 205
Ile Lys Glu Ala Gly Phe Pro Pro Gly Val Val Asn Ile Val Pro Gly
    210                 215                 220
Tyr Gly Pro Thr Ala Gly Ala Ala Ile Ser Ser His Met Asp Ile Asp
225                 230                 235                 240
Lys Val Ala Phe Thr Gly Ser Thr Glu Val Gly Lys Leu Ile Lys Glu
                245                 250                 255
Ala Ala Gly Lys Ser Asn Leu Lys Arg Val Thr Leu Glu Leu Gly Gly
            260                 265                 270
Lys Ser Pro Cys Ile Val Leu Ala Asp Ala Asp Leu Asp Asn Ala Val
        275                 280                 285
Glu Phe Ala His His Gly Val Phe Tyr His Gln Gly Gln Cys Cys Ile
    290                 295                 300
Ala Ala Ser Arg Ile Phe Val Glu Glu Ser Ile Tyr Asp Glu Phe Val
305                 310                 315                 320
Arg Arg Ser Val Glu Arg Ala Lys Lys Tyr Ile Leu Gly Asn Pro Leu
                325                 330                 335
Thr Pro Gly Val Thr Gln Gly Pro Gln Ile Asp Lys Glu Gln Tyr Asp
            340                 345                 350
Lys Ile Leu Asp Leu Ile Glu Ser Gly Lys Lys Glu Gly Ala Lys Leu
        355                 360                 365
Glu Cys Gly Gly Gly Pro Trp Gly Asn Lys Gly Tyr Phe Val Gln Pro
    370                 375                 380
Thr Val Phe Ser Asn Val Thr Asp Glu Met Arg Ile Ala Lys Glu Glu
385                 390                 395                 400
Ile Phe Gly Pro Val Gln Gln Ile Met Lys Phe Lys Ser Leu Asp Asp
                405                 410                 415
Val Ile Lys Arg Ala Asn Asn Thr Phe Tyr Gly Leu Ser Ala Gly Val
            420                 425                 430
Phe Thr Lys Asp Ile Asp Lys Ala Ile Thr Ile Ser Ser Ala Leu Gln
        435                 440                 445
Ala Gly Thr Val Trp Val Asn Cys Tyr Gly Val Val Ser Ala Gln Cys
    450                 455                 460
Pro Phe Gly Gly Phe Lys Met Ser Gly Asn Gly Arg Glu Leu Gly Glu
465                 470                 475                 480
Tyr Gly Phe His Glu Tyr Thr Glu Val Lys Thr Val Thr Val Lys Ile
                485                 490                 495
Ser Gln Lys Asn Ser
            500
```

<210> 23
<211> 3257
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (136)...(2199)

<400> 23
aacaggcgtg acgccagttc taaacttgaa acaaaacaaa acttcaaagt acaccaaaat 60
agaacctcct taaagcataa atctcacgga gggtctcggc cgccagtgga aggagccacc 120
gcccccgccc cgacc atg gcc gag gag ctg gtc tta gag agg tgt gat ctg 171
Met Ala Glu Glu Leu Val Leu Glu Arg Cys Asp Leu

```
                    1               5                  10

gag ctg gag acc aat ggc cga gac cac cac acg gcc gac ctg tgc cgg   219
Glu Leu Glu Thr Asn Gly Arg Asp His His Thr Ala Asp Leu Cys Arg
        15                  20                  25

gag aag ctg gtg gtg cga cgg ggc cag ccc ttc tgg ctg acc ctg cac   267
Glu Lys Leu Val Val Arg Arg Gly Gln Pro Phe Trp Leu Thr Leu His
     30                  35                  40

ttt gag ggc cgc aac tac cag gcc agt gta gac agt ctc acc ttc agt   315
Phe Glu Gly Arg Asn Tyr Gln Ala Ser Val Asp Ser Leu Thr Phe Ser
 45                  50                  55                  60

gtc gtg acc ggc cca gcc cct agc cag gag gcc ggg acc aag gcc cgt   363
Val Val Thr Gly Pro Ala Pro Ser Gln Glu Ala Gly Thr Lys Ala Arg
                65                  70                  75

ttt cca cta aga gat gct gtg gag gag ggt gac tgg aca gcc acc gtg   411
Phe Pro Leu Arg Asp Ala Val Glu Glu Gly Asp Trp Thr Ala Thr Val
            80                  85                  90

gtg gac cag caa gac tgc acc ctc tcg ctg cag ctc acc acc ccg gcc   459
Val Asp Gln Gln Asp Cys Thr Leu Ser Leu Gln Leu Thr Thr Pro Ala
        95                  100                 105

aac gcc ccc atc ggc ctg tat cgc ctc agc ctg gag gcc tcc act ggc   507
Asn Ala Pro Ile Gly Leu Tyr Arg Leu Ser Leu Glu Ala Ser Thr Gly
    110                 115                 120

tac cag gga tcc agc ttt gtg ctg ggc cac ttc att ttg ctc ttc aac   555
Tyr Gln Gly Ser Ser Phe Val Leu Gly His Phe Ile Leu Leu Phe Asn
125                 130                 135                 140

gcc tgg tgc cca gcg gat gct gtg tac ctg gac tcg gaa gag gag cgg   603
Ala Trp Cys Pro Ala Asp Ala Val Tyr Leu Asp Ser Glu Glu Glu Arg
                145                 150                 155

cag gag tat gtc ctc acc cag cag ggc ttt atc tac cag ggc tcg gcc   651
Gln Glu Tyr Val Leu Thr Gln Gln Gly Phe Ile Tyr Gln Gly Ser Ala
            160                 165                 170

aag ttc atc aag aac ata cct tgg aat ttt ggg cag ttt caa gat ggg   699
Lys Phe Ile Lys Asn Ile Pro Trp Asn Phe Gly Gln Phe Gln Asp Gly
        175                 180                 185

atc cta gac atc tgc ctg atc ctt cta gat gtc aac ccc aag ttc ctg   747
Ile Leu Asp Ile Cys Leu Ile Leu Leu Asp Val Asn Pro Lys Phe Leu
    190                 195                 200

aag aac gcc ggc cgt gac tgc tcc cgg cgc agc agc ccc gtc tac gtg   795
Lys Asn Ala Gly Arg Asp Cys Ser Arg Arg Ser Ser Pro Val Tyr Val
205                 210                 215                 220

ggc cgg gtg ggt agt ggc atg gtc aac tgc aac gat gac cag ggt gtg   843
Gly Arg Val Gly Ser Gly Met Val Asn Cys Asn Asp Asp Gln Gly Val
                225                 230                 235

ctg ctg gga cgc tgg gac aac aac tac ggg gac ggc gtc agc ccc atg   891
Leu Leu Gly Arg Trp Asp Asn Asn Tyr Gly Asp Gly Val Ser Pro Met
            240                 245                 250
```

```
tcc tgg atc ggc agc gtg gac atc ctg cgg cgc tgg aag aac cac ggc   939
Ser Trp Ile Gly Ser Val Asp Ile Leu Arg Arg Trp Lys Asn His Gly
        255                 260                 265

tgc cag cgc gtc aag tat ggc cag tgc tgg gtc ttc gcc gcc gtg gcc   987
Cys Gln Arg Val Lys Tyr Gly Gln Cys Trp Val Phe Ala Ala Val Ala
    270                 275                 280

tgc aca gtg ctg agg tgc cta ggc atc cct acc cgc gtc gtg acc aac   1035
Cys Thr Val Leu Arg Cys Leu Gly Ile Pro Thr Arg Val Val Thr Asn
285                 290                 295                 300

tac aac tcg gcc cat gac cag aac agc aac ctt ctc atc gag tac ttc   1083
Tyr Asn Ser Ala His Asp Gln Asn Ser Asn Leu Leu Ile Glu Tyr Phe
                305                 310                 315

cgc aat gag ttt ggg gag atc cag ggt gac aag agc gag atg atc tgg   1131
Arg Asn Glu Phe Gly Glu Ile Gln Gly Asp Lys Ser Glu Met Ile Trp
            320                 325                 330

aac ttc cac tgc tgg gtg gag tcg tgg atg acc agg ccg gac ctg cag   1179
Asn Phe His Cys Trp Val Glu Ser Trp Met Thr Arg Pro Asp Leu Gln
        335                 340                 345

ccg ggg tac gag ggc tgg cag gcc ctg gac cca acg ccc cag gag aag   1227
Pro Gly Tyr Glu Gly Trp Gln Ala Leu Asp Pro Thr Pro Gln Glu Lys
    350                 355                 360

agc gaa gga acg tac tgc tgt ggc cca gtt cca gtt cgt gcc atc aag   1275
Ser Glu Gly Thr Tyr Cys Cys Gly Pro Val Pro Val Arg Ala Ile Lys
365                 370                 375                 380

gag ggc gac ctg agc acc aag tac gat gcg ccc ttt gtc ttt gcg gag   1323
Glu Gly Asp Leu Ser Thr Lys Tyr Asp Ala Pro Phe Val Phe Ala Glu
                385                 390                 395

gtc aat gcc gac gtg gta gac tgg atc cag cag gac gat ggg tct gtg   1371
Val Asn Ala Asp Val Val Asp Trp Ile Gln Gln Asp Asp Gly Ser Val
            400                 405                 410

cac aaa tcc atc aac cgt tcc ctg atc gtt ggg ctg aag atc agc act   1419
His Lys Ser Ile Asn Arg Ser Leu Ile Val Gly Leu Lys Ile Ser Thr
        415                 420                 425

aag agc gtg ggc cga gac gag cgg gag gat atc acc cac acc tac aaa   1467
Lys Ser Val Gly Arg Asp Glu Arg Glu Asp Ile Thr His Thr Tyr Lys
    430                 435                 440

tac cca gag ggg tcc tca gag gag agg gag gcc ttc aca agg gcg aac   1515
Tyr Pro Glu Gly Ser Ser Glu Glu Arg Glu Ala Phe Thr Arg Ala Asn
445                 450                 455                 460

cac ctg aac aaa ctg gcc gag aag gag gag aca ggg atg gcc atg cgg   1563
His Leu Asn Lys Leu Ala Glu Lys Glu Glu Thr Gly Met Ala Met Arg
                465                 470                 475

atc cgt gtg ggc cag agc atg aac atg ggc agt gac ttt gac gtc ttt   1611
Ile Arg Val Gly Gln Ser Met Asn Met Gly Ser Asp Phe Asp Val Phe
            480                 485                 490
```

```
gcc cac atc acc aac aac acc gct gag gag tac gtc tgc cgc ctc ctg   1659
Ala His Ile Thr Asn Asn Thr Ala Glu Glu Tyr Val Cys Arg Leu Leu
        495                 500                 505

ctc tgt gcc cgc acc gtc agc tac aat ggg atc ttg ggg ccc gag tgt   1707
Leu Cys Ala Arg Thr Val Ser Tyr Asn Gly Ile Leu Gly Pro Glu Cys
    510                 515                 520

ggc acc aag tac ctg ctc aac cta acc ctg gag cct ttc tct gag aag   1755
Gly Thr Lys Tyr Leu Leu Asn Leu Thr Leu Glu Pro Phe Ser Glu Lys
525                 530                 535                 540

agc gtt cct ctt tgc atc ctc tat gag aaa tac cgt gac tgc ctt acg   1803
Ser Val Pro Leu Cys Ile Leu Tyr Glu Lys Tyr Arg Asp Cys Leu Thr
                545                 550                 555

gag tcc aac ctc atc aag gtg cgg gcc ctc ctc gtg gag cca gtt atc   1851
Glu Ser Asn Leu Ile Lys Val Arg Ala Leu Leu Val Glu Pro Val Ile
            560                 565                 570

aac agc tac ctg ctg gct gag agg gac ctc tac ctg gag aat cca gaa   1899
Asn Ser Tyr Leu Leu Ala Glu Arg Asp Leu Tyr Leu Glu Asn Pro Glu
        575                 580                 585

atc aag atc cgg atc ctt ggg gag ccc aag cag aaa cgc aag ctg gtg   1947
Ile Lys Ile Arg Ile Leu Gly Glu Pro Lys Gln Lys Arg Lys Leu Val
    590                 595                 600

gct gag gtg tcc ctg cag aac ccg ctc cct gtg gcc ctg gaa ggc tgc   1995
Ala Glu Val Ser Leu Gln Asn Pro Leu Pro Val Ala Leu Glu Gly Cys
605                 610                 615                 620

acc ttc act gtg gag ggg gcc ggc ctg act gag gag cag aag acg gtg   2043
Thr Phe Thr Val Glu Gly Ala Gly Leu Thr Glu Glu Gln Lys Thr Val
                625                 630                 635

gag atc cca gac ccc gtg gag gca ggg gag gaa gtt aag gtg aga atg   2091
Glu Ile Pro Asp Pro Val Glu Ala Gly Glu Glu Val Lys Val Arg Met
            640                 645                 650

gac ctc gtg ccg ctc cac atg ggc ctc cac aag ctg gtg gtg aac ttc   2139
Asp Leu Val Pro Leu His Met Gly Leu His Lys Leu Val Val Asn Phe
        655                 660                 665

gag agc gac aag ctg aag gct gtg aag ggc ttc cgg aat gtc atc att   2187
Glu Ser Asp Lys Leu Lys Ala Val Lys Gly Phe Arg Asn Val Ile Ile
    670                 675                 680

ggc ccc gcc taa gggacccctg ctcccagcct gctgagagcc cccaccttga       2239
Gly Pro Ala  *
685

tcccaatcct tatcccaagc tagtgagcaa aatatgcccc ttattgggcc ccagacccca 2299
gggcagggtg ggcagcctat gggggctctc ggaaatggaa tgtgcccctg gcccatctca 2359
gcctcctgag cctgtgggtc cccactcacc ccctttgctg tgaggaatgc tctgtgccag 2419
aaacagtggg agccctgacc tgtgctgact ggggctgggg tgagagagga aagacctaca 2479
ttccctctcc tgcccagatg ccctttggaa agccattgac cacccaccat attgtttgat 2539
ctacttcata gctccttgga gcaggcaaaa aagggacagc atgcccttgg ctggatcagg 2599
aatccagctc cctagactgc atcccgtacc tcttcccatg actgcaccca gctccagggg 2659
cccttgggac acccagagct gggtggggac agtgataggc ccaaggtccc ctccacatcc 2719
cagcagccca agcttaatag ccctcccccc caacctcacc attgtgaagc acctactatg 2779
```

tgctgggtgc ctcccacact tgctggggct cacggggcct ccaacccatt taatcaccat 2839
gggaaactgt tgtgggcgct gcttccagga taaggagact gaggcttaga gagaggaggc 2899
agcccccctcc acaccagtgg cctcgtggtt ataagcaagg ctgggtaatg tgaaggccca 2959
agagcagagt ctgggcctct gactctgagt ccactgctcc atttataacc ccagcctgac 3019
ctgagactgt cgcagaggct gtctggggcc tttatcaaaa aaagactcag ccaagacaag 3079
gaggtagaga ggggactggg ggactgggag tcagagccct ggctgggttc aggtcccacg 3139
tctggccagc gactgccttc tcctctctgg gcctttgttt ccttgttggt cagaggagtg 3199
attgaacctg ctcatctcca aggatcctct ccactccatg tttgcaatac acaattcc 3257

<210> 24

<211> 687
<212> PRT
<213> Homo sapiens

<400> 24
Met Ala Glu Glu Leu Val Leu Glu Arg Cys Asp Leu Glu Leu Glu Thr
1 5 10 15
Asn Gly Arg Asp His His Thr Ala Asp Leu Cys Arg Glu Lys Leu Val
20 25 30
Val Arg Arg Gly Gln Pro Phe Trp Leu Thr Leu His Phe Glu Gly Arg
35 40 45
Asn Tyr Gln Ala Ser Val Asp Ser Leu Thr Phe Ser Val Val Thr Gly
50 55 60
Pro Ala Pro Ser Gln Glu Ala Gly Thr Lys Ala Arg Phe Pro Leu Arg
65 70 75 80
Asp Ala Val Glu Glu Gly Asp Trp Thr Ala Thr Val Val Asp Gln Gln
85 90 95
Asp Cys Thr Leu Ser Leu Gln Leu Thr Thr Pro Ala Asn Ala Pro Ile
100 105 110
Gly Leu Tyr Arg Leu Ser Leu Glu Ala Ser Thr Gly Tyr Gln Gly Ser
115 120 125
Ser Phe Val Leu Gly His Phe Ile Leu Leu Phe Asn Ala Trp Cys Pro
130 135 140
Ala Asp Ala Val Tyr Leu Asp Ser Glu Glu Glu Arg Gln Glu Tyr Val
145 150 155 160
Leu Thr Gln Gln Gly Phe Ile Tyr Gln Gly Ser Ala Lys Phe Ile Lys
165 170 175
Asn Ile Pro Trp Asn Phe Gly Gln Phe Gln Asp Gly Ile Leu Asp Ile
180 185 190
Cys Leu Ile Leu Leu Asp Val Asn Pro Lys Phe Leu Lys Asn Ala Gly
195 200 205
Arg Asp Cys Ser Arg Arg Ser Ser Pro Val Tyr Val Gly Arg Val Gly
210 215 220
Ser Gly Met Val Asn Cys Asn Asp Asp Gln Gly Val Leu Leu Gly Arg
225 230 235 240
Trp Asp Asn Asn Tyr Gly Asp Gly Val Ser Pro Met Ser Trp Ile Gly
245 250 255
Ser Val Asp Ile Leu Arg Arg Trp Lys Asn His Gly Cys Gln Arg Val
260 265 270
Lys Tyr Gly Gln Cys Trp Val Phe Ala Ala Val Ala Cys Thr Val Leu
275 280 285
Arg Cys Leu Gly Ile Pro Thr Arg Val Val Thr Asn Tyr Asn Ser Ala
290 295 300
His Asp Gln Asn Ser Asn Leu Leu Ile Glu Tyr Phe Arg Asn Glu Phe
305 310 315 320
Gly Glu Ile Gln Gly Asp Lys Ser Glu Met Ile Trp Asn Phe His Cys
325 330 335
Trp Val Glu Ser Trp Met Thr Arg Pro Asp Leu Gln Pro Gly Tyr Glu
340 345 350
Gly Trp Gln Ala Leu Asp Pro Thr Pro Gln Glu Lys Ser Glu Gly Thr

```
        355                 360                 365
Tyr Cys Cys Gly Pro Val Pro Val Arg Ala Ile Lys Glu Gly Asp Leu
    370                 375                 380
Ser Thr Lys Tyr Asp Ala Pro Phe Val Phe Ala Glu Val Asn Ala Asp
385                 390                 395                 400
Val Val Asp Trp Ile Gln Gln Asp Asp Gly Ser Val His Lys Ser Ile
                405                 410                 415
Asn Arg Ser Leu Ile Val Gly Leu Lys Ile Ser Thr Lys Ser Val Gly
            420                 425                 430
Arg Asp Glu Arg Glu Asp Ile Thr His Thr Tyr Lys Tyr Pro Glu Gly
        435                 440                 445
Ser Ser Glu Glu Arg Glu Ala Phe Thr Arg Ala Asn His Leu Asn Lys
    450                 455                 460
Leu Ala Glu Lys Glu Glu Thr Gly Met Ala Met Arg Ile Arg Val Gly
465                 470                 475                 480
Gln Ser Met Asn Met Gly Ser Asp Phe Asp Val Phe Ala His Ile Thr
                485                 490                 495
Asn Asn Thr Ala Glu Glu Tyr Val Cys Arg Leu Leu Leu Cys Ala Arg
            500                 505                 510
Thr Val Ser Tyr Asn Gly Ile Leu Gly Pro Glu Cys Gly Thr Lys Tyr
        515                 520                 525
Leu Leu Asn Leu Thr Leu Glu Pro Phe Ser Glu Lys Ser Val Pro Leu
    530                 535                 540
Cys Ile Leu Tyr Glu Lys Tyr Arg Asp Cys Leu Thr Glu Ser Asn Leu
545                 550                 555                 560
Ile Lys Val Arg Ala Leu Leu Val Glu Pro Val Ile Asn Ser Tyr Leu
                565                 570                 575
Leu Ala Glu Arg Asp Leu Tyr Leu Glu Asn Pro Glu Ile Lys Ile Arg
            580                 585                 590
Ile Leu Gly Glu Pro Lys Gln Lys Arg Lys Leu Val Ala Glu Val Ser
        595                 600                 605
Leu Gln Asn Pro Leu Pro Val Ala Leu Glu Gly Cys Thr Phe Thr Val
    610                 615                 620
Glu Gly Ala Gly Leu Thr Glu Glu Gln Lys Thr Val Glu Ile Pro Asp
625                 630                 635                 640
Pro Val Glu Ala Gly Glu Glu Val Lys Val Arg Met Asp Leu Val Pro
                645                 650                 655
Leu His Met Gly Leu His Lys Leu Val Val Asn Phe Glu Ser Asp Lys
            660                 665                 670
Leu Lys Ala Val Lys Gly Phe Arg Asn Val Ile Ile Gly Pro Ala
        675                 680                 685
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<210> 25
<211> 1061
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (11)...(1051)

<400> 25

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ggccaccacc atg gat aca ggc ccc gac cag tcc tac ttc tcc ggc aat    49
           Met Asp Thr Gly Pro Asp Gln Ser Tyr Phe Ser Gly Asn
            1               5                  10

cac tgg ttc gtc ttc tcg gtg tac ctt ctc act ttc ctg gtg ggg ctc    97
His Trp Phe Val Phe Ser Val Tyr Leu Leu Thr Phe Leu Val Gly Leu
     15                  20                  25
```

```
ccc ctc aac ctg ctg gcc ctg gtg gtc ttc gtg ggc aag ctg cag cgc   145
Pro Leu Asn Leu Leu Ala Leu Val Val Phe Val Gly Lys Leu Gln Arg
 30                  35                  40                  45

cgc ccg gtg gcc gtg gac gtg ctc ctg ctc aac ctg acc gcc tcg gac   193
Arg Pro Val Ala Val Asp Val Leu Leu Leu Asn Leu Thr Ala Ser Asp
                50                  55                  60

ctg ctc ctg ctg ctg ttc ctg cct ttc cgc atg gtg gag gca gcc aat   241
Leu Leu Leu Leu Leu Phe Leu Pro Phe Arg Met Val Glu Ala Ala Asn
            65                  70                  75

ggc atg cac tgg ccc ctg ccc ttc atc ctc tgc cca ctc tct gga ttc   289
Gly Met His Trp Pro Leu Pro Phe Ile Leu Cys Pro Leu Ser Gly Phe
        80                  85                  90

atc ttc ttc acc acc atc tat ctc acc gcc ctc ttc ctg gca gct gtg   337
Ile Phe Phe Thr Thr Ile Tyr Leu Thr Ala Leu Phe Leu Ala Ala Val
    95                  100                 105

agc att gaa cgc ttc ctg agt gtg gcc cac cca ctg tgg tac aag acc   385
Ser Ile Glu Arg Phe Leu Ser Val Ala His Pro Leu Trp Tyr Lys Thr
110                 115                 120                 125

cgg ccg agg ctg ggg cag gca ggt ctg gtg agt gtg gcc tgc tgg ctg   433
Arg Pro Arg Leu Gly Gln Ala Gly Leu Val Ser Val Ala Cys Trp Leu
                130                 135                 140

ttg gcc tct gct cac tgc agc gtg gtc tac gtc ata gaa ttc tca ggg   481
Leu Ala Ser Ala His Cys Ser Val Val Tyr Val Ile Glu Phe Ser Gly
            145                 150                 155

gac atc tcc cac agc cag ggc acc aat ggg acc tgc tac ctg gag ttc   529
Asp Ile Ser His Ser Gln Gly Thr Asn Gly Thr Cys Tyr Leu Glu Phe
        160                 165                 170

cgg aag gac cag cta gcc atc ctc ctg ccc gtg cgg ctg gag atg gct   577
Arg Lys Asp Gln Leu Ala Ile Leu Leu Pro Val Arg Leu Glu Met Ala
    175                 180                 185

gtg gtc ctc ttt gtg gtc ccg ctg atc atc acc agc tac tgc tac agc   625
Val Val Leu Phe Val Val Pro Leu Ile Ile Thr Ser Tyr Cys Tyr Ser
190                 195                 200                 205

cgc ctg gtg tgg atc ctc ggc aga ggg ggc agc cac cgc cgg cag agg   673
Arg Leu Val Trp Ile Leu Gly Arg Gly Gly Ser His Arg Arg Gln Arg
                210                 215                 220

agg gtg gcg ggg ctg ttg gcg gcc acg ctg ctc aac ttc ctt gtc tgc   721
Arg Val Ala Gly Leu Leu Ala Ala Thr Leu Leu Asn Phe Leu Val Cys
            225                 230                 235

ttt ggg ccc tac aac gtg tcc cat gtc gtg ggc tat atc tgc ggt gaa   769
Phe Gly Pro Tyr Asn Val Ser His Val Val Gly Tyr Ile Cys Gly Glu
        240                 245                 250

agc ccg gca tgg agg atc tac gtg acg ctt ctc agc acc ctg aac tcc   817
Ser Pro Ala Trp Arg Ile Tyr Val Thr Leu Leu Ser Thr Leu Asn Ser
    255                 260                 265

tgt gtc gac ccc ttt gtc tac tac ttc tcc tcc tcc ggg ttc caa gcc   865
```

```
Cys Val Asp Pro Phe Val Tyr Tyr Phe Ser Ser Ser Gly Phe Gln Ala
270                 275                 280                 285

gac ttt cat gag ctg ctg agg agg ttg tgt ggg ctc tgg ggc cag tgg   913
Asp Phe His Glu Leu Leu Arg Arg Leu Cys Gly Leu Trp Gly Gln Trp
                290                 295                 300

cag cag gag agc agc atg gag ctg aag gag cag aag gga ggg gag gag   961
Gln Gln Glu Ser Ser Met Glu Leu Lys Glu Gln Lys Gly Gly Glu Glu
            305                 310                 315

cag aga gcg gac cga cca gct gaa aga aag acc agt gaa cac tca cag   1009
Gln Arg Ala Asp Arg Pro Ala Glu Arg Lys Thr Ser Glu His Ser Gln
        320                 325                 330

ggc tgt gga act ggt ggc cag gtg gcc tgt gct gaa agc tag           1051
Gly Cys Gly Thr Gly Gly Gln Val Ala Cys Ala Glu Ser  *
    335                 340                 345

gtcctccggg                                                       1061

<210> 26
<211> 346
<212> PRT
<213> Homo sapiens

<400> 26
Met Asp Thr Gly Pro Asp Gln Ser Tyr Phe Ser Gly Asn His Trp Phe
 1               5                  10                  15
Val Phe Ser Val Tyr Leu Leu Thr Phe Leu Val Gly Leu Pro Leu Asn
            20                  25                  30
Leu Leu Ala Leu Val Val Phe Val Gly Lys Leu Gln Arg Arg Pro Val
        35                  40                  45
Ala Val Asp Val Leu Leu Leu Asn Leu Thr Ala Ser Asp Leu Leu Leu
    50                  55                  60
Leu Leu Phe Leu Pro Phe Arg Met Val Glu Ala Ala Asn Gly Met His
65                  70                  75                  80
Trp Pro Leu Pro Phe Ile Leu Cys Pro Leu Ser Gly Phe Ile Phe Phe
                85                  90                  95
Thr Thr Ile Tyr Leu Thr Ala Leu Phe Leu Ala Ala Val Ser Ile Glu
            100                 105                 110
Arg Phe Leu Ser Val Ala His Pro Leu Trp Tyr Lys Thr Arg Pro Arg
        115                 120                 125
Leu Gly Gln Ala Gly Leu Val Ser Val Ala Cys Trp Leu Leu Ala Ser
    130                 135                 140
Ala His Cys Ser Val Val Tyr Val Ile Glu Phe Ser Gly Asp Ile Ser
145                 150                 155                 160
His Ser Gln Gly Thr Asn Gly Thr Cys Tyr Leu Glu Phe Arg Lys Asp
                165                 170                 175
Gln Leu Ala Ile Leu Leu Pro Val Arg Leu Glu Met Ala Val Val Leu
            180                 185                 190
Phe Val Val Pro Leu Ile Ile Thr Ser Tyr Cys Tyr Ser Arg Leu Val
        195                 200                 205
Trp Ile Leu Gly Arg Gly Gly Ser His Arg Arg Gln Arg Arg Val Ala
    210                 215                 220
Gly Leu Leu Ala Ala Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro
225                 230                 235                 240
Tyr Asn Val Ser His Val Val Gly Tyr Ile Cys Gly Glu Ser Pro Ala
                245                 250                 255
Trp Arg Ile Tyr Val Thr Leu Leu Ser Thr Leu Asn Ser Cys Val Asp
            260                 265                 270
```

```
Pro Phe Val Tyr Tyr Phe Ser Ser Ser Gly Phe Gln Ala Asp Phe His
        275                 280                 285
Glu Leu Leu Arg Arg Leu Cys Gly Leu Trp Gly Gln Trp Gln Gln Glu
    290                 295                 300
Ser Ser Met Glu Leu Lys Glu Gln Lys Gly Gly Glu Glu Gln Arg Ala
305                 310                 315                 320
Asp Arg Pro Ala Glu Arg Lys Thr Ser Glu His Ser Gln Gly Cys Gly
                325                 330                 335
Thr Gly Gly Gln Val Ala Cys Ala Glu Ser
            340                 345
```

<210> 27
<211> 1013
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (11)...(1003)

<400> 27

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cccctccagg atg ctg ccg gac tgg aag agc tcc ttg atc ctc atg gct    49
              Met Leu Pro Asp Trp Lys Ser Ser Leu Ile Leu Met Ala
               1               5                   10

tac atc atc atc ttc ctc act ggc ctc cct gcc aac ctc ctg gcc ctg    97
Tyr Ile Ile Ile Phe Leu Thr Gly Leu Pro Ala Asn Leu Leu Ala Leu
     15                  20                  25

cgg gcc ttt gtg ggg cgg atc cgc cag ccc cag cct gca cct gtg cac   145
Arg Ala Phe Val Gly Arg Ile Arg Gln Pro Gln Pro Ala Pro Val His
 30                  35                  40                  45

atc ctc ctg ctg agc ctg acg ctg gcc gac ctc ctc ctg ctg ctg ctg   193
Ile Leu Leu Leu Ser Leu Thr Leu Ala Asp Leu Leu Leu Leu Leu Leu
                 50                  55                  60

ctg ccc ttc aag atc atc gag gct gcg tcg aac ttc cgc tgg tac ctg   241
Leu Pro Phe Lys Ile Ile Glu Ala Ala Ser Asn Phe Arg Trp Tyr Leu
             65                  70                  75

ccc aag gtc gtc tgc gcc ctc acg agt ttt ggc ttc tac agc agc atc   289
Pro Lys Val Val Cys Ala Leu Thr Ser Phe Gly Phe Tyr Ser Ser Ile
         80                  85                  90

tac tgc agc acg tgg ctc ctg gcg ggc atc agc atc gag cgc tac ctg   337
Tyr Cys Ser Thr Trp Leu Leu Ala Gly Ile Ser Ile Glu Arg Tyr Leu
     95                  100                 105

gga gtg gct ttc ccc gtg cag tac aag ctc tcc cgc cgg cct ctg tat   385
Gly Val Ala Phe Pro Val Gln Tyr Lys Leu Ser Arg Arg Pro Leu Tyr
110                 115                 120                 125

gga gtg att gca gct ctg gtg gcc tgg gtt atg tcc ttt ggt cac tgc   433
Gly Val Ile Ala Ala Leu Val Ala Trp Val Met Ser Phe Gly His Cys
                130                 135                 140

acc atc gtg atc atc gtt caa tac ttg aac acg act gag cag gtc aga   481
Thr Ile Val Ile Ile Val Gln Tyr Leu Asn Thr Thr Glu Gln Val Arg
            145                 150                 155
```

```
agt ggc aat gaa att acc tgc tac gag aac ttc acc gat aac cag ttg   529
Ser Gly Asn Glu Ile Thr Cys Tyr Glu Asn Phe Thr Asp Asn Gln Leu
        160                 165                 170

gac gtg gtg ctg ccc gtg cgg ctg gag ctg tgc ctg gtg ctc ttc ttc   577
Asp Val Val Leu Pro Val Arg Leu Glu Leu Cys Leu Val Leu Phe Phe
    175                 180                 185

atc ccc atg gca gtc acc atc ttc tgc tac tgg cgt ttt gtg tgg atc   625
Ile Pro Met Ala Val Thr Ile Phe Cys Tyr Trp Arg Phe Val Trp Ile
190                 195                 200                 205

atg ctc tcc cag ccc ctt gtg ggg gcc cag agg cgg cgc cga gcc gtg   673
Met Leu Ser Gln Pro Leu Val Gly Ala Gln Arg Arg Arg Arg Ala Val
                210                 215                 220

ggg ctg gct gtg gtg acg ctg ctc aat ttc ctg gtg tgc ttc gga cct   721
Gly Leu Ala Val Val Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro
            225                 230                 235

tac aac gtg tcc cac ctg gtg ggg tat cac cag aga aaa agc ccc tgg   769
Tyr Asn Val Ser His Leu Val Gly Tyr His Gln Arg Lys Ser Pro Trp
        240                 245                 250

tgg cgg tca ata gcc gtg gtg ttc agt tca ctc aac gcc agt ctg gac   817
Trp Arg Ser Ile Ala Val Val Phe Ser Ser Leu Asn Ala Ser Leu Asp
    255                 260                 265

ccc ctg ctc ttc tat ttc tct tct tca gtg gtg cgc agg gca ttt ggg   865
Pro Leu Leu Phe Tyr Phe Ser Ser Ser Val Val Arg Arg Ala Phe Gly
270                 275                 280                 285

aga ggg ctg cag gtg ctg cgg aat cag ggc tcc tcc ctg ttg gga cgc   913
Arg Gly Leu Gln Val Leu Arg Asn Gln Gly Ser Ser Leu Leu Gly Arg
                290                 295                 300

aga ggc aaa gac aca gca gag ggg aca aat gag gac agg ggt gtg ggt   961
Arg Gly Lys Asp Thr Ala Glu Gly Thr Asn Glu Asp Arg Gly Val Gly
            305                 310                 315

caa gga gaa ggg atg cca agt tcg gac ttc act aca gag tag          1003
Gln Gly Glu Gly Met Pro Ser Ser Asp Phe Thr Thr Glu  *
        320                 325                 330

cagtttccct                                                      1013

<210> 28
<211> 330
<212> PRT
<213> Homo sapiens

<400> 28
Met Leu Pro Asp Trp Lys Ser Ser Leu Ile Leu Met Ala Tyr Ile Ile
 1               5                  10                  15
Ile Phe Leu Thr Gly Leu Pro Ala Asn Leu Leu Ala Leu Arg Ala Phe
            20                  25                  30
Val Gly Arg Ile Arg Gln Pro Gln Pro Ala Pro Val His Ile Leu Leu
        35                  40                  45
Leu Ser Leu Thr Leu Ala Asp Leu Leu Leu Leu Leu Leu Leu Pro Phe
    50                  55                  60
```

```
Lys Ile Ile Glu Ala Ala Ser Asn Phe Arg Trp Tyr Leu Pro Lys Val
65                  70                  75                  80
Val Cys Ala Leu Thr Ser Phe Gly Phe Tyr Ser Ser Ile Tyr Cys Ser
                85                  90                  95
Thr Trp Leu Leu Ala Gly Ile Ser Ile Glu Arg Tyr Leu Gly Val Ala
            100                 105                 110
Phe Pro Val Gln Tyr Lys Leu Ser Arg Arg Pro Leu Tyr Gly Val Ile
        115                 120                 125
Ala Ala Leu Val Ala Trp Val Met Ser Phe Gly His Cys Thr Ile Val
    130                 135                 140
Ile Ile Val Gln Tyr Leu Asn Thr Thr Glu Gln Val Arg Ser Gly Asn
145                 150                 155                 160
Glu Ile Thr Cys Tyr Glu Asn Phe Thr Asp Asn Gln Leu Asp Val Val
                165                 170                 175
Leu Pro Val Arg Leu Glu Leu Cys Leu Val Leu Phe Phe Ile Pro Met
            180                 185                 190
Ala Val Thr Ile Phe Cys Tyr Trp Arg Phe Val Trp Ile Met Leu Ser
        195                 200                 205
Gln Pro Leu Val Gly Ala Gln Arg Arg Arg Arg Ala Val Gly Leu Ala
    210                 215                 220
Val Val Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro Tyr Asn Val
225                 230                 235                 240
Ser His Leu Val Gly Tyr His Gln Arg Lys Ser Pro Trp Trp Arg Ser
                245                 250                 255
Ile Ala Val Val Phe Ser Ser Leu Asn Ala Ser Leu Asp Pro Leu Leu
            260                 265                 270
Phe Tyr Phe Ser Ser Ser Val Val Arg Arg Ala Phe Gly Arg Gly Leu
        275                 280                 285
Gln Val Leu Arg Asn Gln Gly Ser Ser Leu Leu Gly Arg Arg Gly Lys
    290                 295                 300
Asp Thr Ala Glu Gly Thr Asn Glu Asp Arg Gly Val Gly Gln Gly Glu
305                 310                 315                 320
Gly Met Pro Ser Ser Asp Phe Thr Thr Glu
                325                 330
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<210> 29
<211> 1982
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (63)...(1460)

<400> 29

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cc atg gga ggg gcc gtg gtg gac gag ggc ccc aca ggc gtc aag gcc    107
   Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala
    1               5                  10                  15

cct gac ggc ggc tgg ggc tgg gcc gtg ctc ttc ggc tgt ttc gtc atc   155
Pro Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile
                20                  25                  30

act ggc ttc tcc tac gcc ttc ccc aag gcc gtc agt gtc ttc ttc aag   203
Thr Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys
            35                  40                  45

gag ctc ata cag gag ttt ggg atc ggc tac agc gac aca gcc tgg atc   251
Glu Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile
```

```
          50                  55                  60

tcc tcc atc ctg ctg gcc atg ctc tac ggg aca ggt ccg ctc tgc agt   299
Ser Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser
     65                  70                  75

gtg tgc gtg aac cgc ttt ggc tgc cgg ccc gtc atg ctt gtg ggg ggt   347
Val Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly
 80                  85                  90                  95

ctc ttt gcg tcg ctg ggc atg gtg gct gcg tcc ttt tgc cgg agc atc   395
Leu Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile
                100                 105                 110

atc cag gtc tac ctc acc act ggg gtc atc acg ggg ttg ggt ttg gca   443
Ile Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala
            115                 120                 125

ctc aac ttc cag ccc tcg ctc atc atg ctg aac cgc tac ttc agc aag   491
Leu Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys
        130                 135                 140

cgg cgc ccc atg gcc aac ggg ctg gcg gca gca ggt agc cct gtc ttc   539
Arg Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe
    145                 150                 155

ctg tgt gcc ctg agc ccg ctg ggg cag ctg ctg cag gac cgc tac ggc   587
Leu Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly
160                 165                 170                 175

tgg cgg ggc ggc ttc ctc atc ctg ggc ggc ctg ctg ctc aac tgc tgc   635
Trp Arg Gly Gly Phe Leu Ile Leu Gly Gly Leu Leu Leu Asn Cys Cys
                180                 185                 190

gtg tgt gcc gca ctc atg agg ccc ctg gtg gtc acg gcc cag ccg ggc   683
Val Cys Ala Ala Leu Met Arg Pro Leu Val Val Thr Ala Gln Pro Gly
            195                 200                 205

tcg ggg ccg ccg cga ccc tcc cgg cgc ctg cta gac ctg agc gtc ttc   731
Ser Gly Pro Pro Arg Pro Ser Arg Arg Leu Leu Asp Leu Ser Val Phe
        210                 215                 220

cgg gac cgc ggc ttt gtg ctt tac gcc gtg gcc gcc tcg gtc atg gtg   779
Arg Asp Arg Gly Phe Val Leu Tyr Ala Val Ala Ala Ser Val Met Val
    225                 230                 235

ctg ggg ctc ttc gtc ccg ccc gtg ttc gtg gtg agc tac gcc aag gac   827
Leu Gly Leu Phe Val Pro Pro Val Phe Val Val Ser Tyr Ala Lys Asp
240                 245                 250                 255

ctg ggc gtg ccc gac acc aag gcc gcc ttc ctg ctc acc atc ctg ggc   875
Leu Gly Val Pro Asp Thr Lys Ala Ala Phe Leu Leu Thr Ile Leu Gly
                260                 265                 270

ttc att gac atc ttc gcg cgg ccg gcc gcg ggc ttc gtg gcg ggg ctt   923
Phe Ile Asp Ile Phe Ala Arg Pro Ala Ala Gly Phe Val Ala Gly Leu
            275                 280                 285

ggg aag gtg cgg ccc tac tcc gtc tac ctc ttc agc ttc tcc atg ttc   971
Gly Lys Val Arg Pro Tyr Ser Val Tyr Leu Phe Ser Phe Ser Met Phe
        290                 295                 300
```

```
ttc aac ggc ctc gcg gac ctg gcg ggc tct acg gcg ggc gac tac ggc   1019
Phe Asn Gly Leu Ala Asp Leu Ala Gly Ser Thr Ala Gly Asp Tyr Gly
    305                 310                 315

ggc ctc gtg gtc ttc tgc atc ttc ttt ggc atc tcc tac ggc atg gtg   1067
Gly Leu Val Val Phe Cys Ile Phe Phe Gly Ile Ser Tyr Gly Met Val
320                 325                 330                 335

ggg gcc ctg cag ttc gag gtg ctc atg gcc atc gtg ggc acc cac aag   1115
Gly Ala Leu Gln Phe Glu Val Leu Met Ala Ile Val Gly Thr His Lys
                340                 345                 350

ttc tcc agt gcc att ggc ctg gtg ctg ctg atg gag gcg gtg gcc gtg   1163
Phe Ser Ser Ala Ile Gly Leu Val Leu Leu Met Glu Ala Val Ala Val
            355                 360                 365

ctc gtc ggg ccc cct tcg gga ggc aaa ctc ctg gat gcg acc cac gtc   1211
Leu Val Gly Pro Pro Ser Gly Gly Lys Leu Leu Asp Ala Thr His Val
        370                 375                 380

tac atg tac gtg ttc atc ctg gcg ggg gcc gag gtg ctc acc tcc tcc   1259
Tyr Met Tyr Val Phe Ile Leu Ala Gly Ala Glu Val Leu Thr Ser Ser
    385                 390                 395

ctg att ttg ctg ctg ggc aac ttc ttc tgc att agg aag aag ccc aaa   1307
Leu Ile Leu Leu Leu Gly Asn Phe Phe Cys Ile Arg Lys Lys Pro Lys
400                 405                 410                 415

gag cca cag cct gag gtg gcg gcc gcg gag gag gag aag ctc cac aag   1355
Glu Pro Gln Pro Glu Val Ala Ala Ala Glu Glu Glu Lys Leu His Lys
                420                 425                 430

cct cct gca gac tcg ggg gtg gac ttg cgg gag gtg gag cat ttc ctg   1403
Pro Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu
            435                 440                 445

aag gct gag cct gag aaa aac ggg gag gtg gtt cac acc ccg gaa aca   1451
Lys Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr
        450                 455                 460

agt gtc tga gtggctgggc ggggccggca ggcacaggga ggaggtacag           1500
Ser Val  *
    465

aagccggcaa cgcttgctat ttattttaca aactggactg gctcaggcag ggccacggct 1560
gggctccagc tgccggccca gcggatcgtc gcccgatcag tgttttgagg gggaaggtgg 1620
cggggtggga accgtgtcat tccagagtgg atctgcggtg aagccaagcc gcaaggttac 1680
aaggcatcct caccaggggc cccgcctgct gctcccaggt ggcctgcggc cactgctatg 1740
ctcaaggacc tggaaaccca tgcttcgaga caacgtgact ttaatgggag ggtgggtggg 1800
ccgcagacag gctggcaggg caggtgctgc gtggggccct ctccagcccg tcctaccctg 1860
ggctcacatg gggcctgtgc ccacccctct tgagtgtctt ggggacagct ctttccaccc 1920
ctggaagatg gaaataaacc tgcgtgtggg tggagtgttc tcgtgccgaa ttcaaaaagc 1980
tt                                                                1982

<210> 30
<211> 465
<212> PRT
<213> Homo sapiens

<400> 30
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Met Gly Gly Ala Val Val Asp Glu Gly Pro Thr Gly Val Lys Ala Pro
 1               5                  10                  15
Asp Gly Gly Trp Gly Trp Ala Val Leu Phe Gly Cys Phe Val Ile Thr
            20                  25                  30
Gly Phe Ser Tyr Ala Phe Pro Lys Ala Val Ser Val Phe Phe Lys Glu
        35                  40                  45
Leu Ile Gln Glu Phe Gly Ile Gly Tyr Ser Asp Thr Ala Trp Ile Ser
    50                  55                  60
Ser Ile Leu Leu Ala Met Leu Tyr Gly Thr Gly Pro Leu Cys Ser Val
65                  70                  75                  80
Cys Val Asn Arg Phe Gly Cys Arg Pro Val Met Leu Val Gly Gly Leu
                85                  90                  95
Phe Ala Ser Leu Gly Met Val Ala Ala Ser Phe Cys Arg Ser Ile Ile
            100                 105                 110
Gln Val Tyr Leu Thr Thr Gly Val Ile Thr Gly Leu Gly Leu Ala Leu
        115                 120                 125
Asn Phe Gln Pro Ser Leu Ile Met Leu Asn Arg Tyr Phe Ser Lys Arg
    130                 135                 140
Arg Pro Met Ala Asn Gly Leu Ala Ala Ala Gly Ser Pro Val Phe Leu
145                 150                 155                 160
Cys Ala Leu Ser Pro Leu Gly Gln Leu Leu Gln Asp Arg Tyr Gly Trp
                165                 170                 175
Arg Gly Gly Phe Leu Ile Leu Gly Gly Leu Leu Leu Asn Cys Cys Val
            180                 185                 190
Cys Ala Ala Leu Met Arg Pro Leu Val Val Thr Ala Gln Pro Gly Ser
        195                 200                 205
Gly Pro Pro Arg Pro Ser Arg Arg Leu Leu Asp Leu Ser Val Phe Arg
    210                 215                 220
Asp Arg Gly Phe Val Leu Tyr Ala Val Ala Ala Ser Val Met Val Leu
225                 230                 235                 240
Gly Leu Phe Val Pro Pro Val Phe Val Val Ser Tyr Ala Lys Asp Leu
                245                 250                 255
Gly Val Pro Asp Thr Lys Ala Ala Phe Leu Leu Thr Ile Leu Gly Phe
            260                 265                 270
Ile Asp Ile Phe Ala Arg Pro Ala Ala Gly Phe Val Ala Gly Leu Gly
        275                 280                 285
Lys Val Arg Pro Tyr Ser Val Tyr Leu Phe Ser Phe Ser Met Phe Phe
    290                 295                 300
Asn Gly Leu Ala Asp Leu Ala Gly Ser Thr Ala Gly Asp Tyr Gly Gly
305                 310                 315                 320
Leu Val Val Phe Cys Ile Phe Phe Gly Ile Ser Tyr Gly Met Val Gly
                325                 330                 335
Ala Leu Gln Phe Glu Val Leu Met Ala Ile Val Gly Thr His Lys Phe
            340                 345                 350
Ser Ser Ala Ile Gly Leu Val Leu Leu Met Glu Ala Val Ala Val Leu
        355                 360                 365
Val Gly Pro Pro Ser Gly Gly Lys Leu Leu Asp Ala Thr His Val Tyr
    370                 375                 380
Met Tyr Val Phe Ile Leu Ala Gly Ala Glu Val Leu Thr Ser Ser Leu
385                 390                 395                 400
Ile Leu Leu Leu Gly Asn Phe Phe Cys Ile Arg Lys Lys Pro Lys Glu
                405                 410                 415
Pro Gln Pro Glu Val Ala Ala Ala Glu Glu Glu Lys Leu His Lys Pro
            420                 425                 430
Pro Ala Asp Ser Gly Val Asp Leu Arg Glu Val Glu His Phe Leu Lys
        435                 440                 445
Ala Glu Pro Glu Lys Asn Gly Glu Val Val His Thr Pro Glu Thr Ser
    450                 455                 460
Val
465
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<210> 31
<211> 1999
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (53)...(1513)

<400> 31
gaattcggca cgagcagaag caacaataat tgtgaaaaat acttcagcag tt atg gac 58
Met Asp
1

tca tct gtc att caa agg aaa aaa gta gct gtc att ggt ggt ggc ttg 106
Ser Ser Val Ile Gln Arg Lys Lys Val Ala Val Ile Gly Gly Gly Leu
5 10 15

gtt ggc tca tta caa gca tgc ttt ctt gca aag agg aat ttc cag att 154
Val Gly Ser Leu Gln Ala Cys Phe Leu Ala Lys Arg Asn Phe Gln Ile
20 25 30

gat gta tat gaa gct agg gaa gat act cga gtg gct acc ttc aca cgt 202
Asp Val Tyr Glu Ala Arg Glu Asp Thr Arg Val Ala Thr Phe Thr Arg
35 40 45 50

gga aga agc att aac tta gcc ctt tct cat aga gga cga caa gcc ttg 250
Gly Arg Ser Ile Asn Leu Ala Leu Ser His Arg Gly Arg Gln Ala Leu
55 60 65

aaa gct gtt ggc ctg gaa gat cag att gta tcc caa ggt att ccc atg 298
Lys Ala Val Gly Leu Glu Asp Gln Ile Val Ser Gln Gly Ile Pro Met
70 75 80

aga gca aga atg atc cac tct ctt tca gga aaa aag tct gca att ccc 346
Arg Ala Arg Met Ile His Ser Leu Ser Gly Lys Lys Ser Ala Ile Pro
85 90 95

tat ggg aca aag tct cag tat att ctt tct gta agc aga gaa aat cta 394
Tyr Gly Thr Lys Ser Gln Tyr Ile Leu Ser Val Ser Arg Glu Asn Leu
100 105 110

aac aag gat cta ttg act gct gct gag aaa tac ccc aat gtg aaa atg 442
Asn Lys Asp Leu Leu Thr Ala Ala Glu Lys Tyr Pro Asn Val Lys Met
115 120 125 130

cac ttt aac cac agg ctg ttg aaa tgt aat cca gag gaa gga atg atc 490
His Phe Asn His Arg Leu Leu Lys Cys Asn Pro Glu Glu Gly Met Ile
135 140 145

aca gtg ctt gga tct gac aaa gtt ccc aaa gat gtc act tgt gac ctc 538
Thr Val Leu Gly Ser Asp Lys Val Pro Lys Asp Val Thr Cys Asp Leu
150 155 160

att gta gga tgt gat gga gcc tat tca act gtc aga tct cac ctg atg 586
Ile Val Gly Cys Asp Gly Ala Tyr Ser Thr Val Arg Ser His Leu Met
165 170 175

aag aaa cct cgc ttt gat tac agt cag cag tac att cct cat ggg tac 634
Lys Lys Pro Arg Phe Asp Tyr Ser Gln Gln Tyr Ile Pro His Gly Tyr

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    180                 185                 190

atg gag ttg act att cca cct aag aac gga gat tat gcc atg gaa cct   682
Met Glu Leu Thr Ile Pro Pro Lys Asn Gly Asp Tyr Ala Met Glu Pro
195                 200                 205                 210

aat tat ctg cat att tgg cct aga aat acc ttt atg atg att gca ctt   730
Asn Tyr Leu His Ile Trp Pro Arg Asn Thr Phe Met Met Ile Ala Leu
                215                 220                 225

cct aac atg aac aaa tca ttc aca tgt act ttg ttc atg ccc ttt gaa   778
Pro Asn Met Asn Lys Ser Phe Thr Cys Thr Leu Phe Met Pro Phe Glu
            230                 235                 240

gag ttt gaa aaa ctt cta acc agt aat gat gtg gta gat ttc ttc cag   826
Glu Phe Glu Lys Leu Leu Thr Ser Asn Asp Val Val Asp Phe Phe Gln
        245                 250                 255

aaa tac ttt ccg gat gcc atc cct cta att gga gag aaa ctc cta gtg   874
Lys Tyr Phe Pro Asp Ala Ile Pro Leu Ile Gly Glu Lys Leu Leu Val
    260                 265                 270

caa gat ttc ttc ctg ttg cct gcc cag ccc atg ata tct gta aag tgc   922
Gln Asp Phe Phe Leu Leu Pro Ala Gln Pro Met Ile Ser Val Lys Cys
275                 280                 285                 290

tct tca ttt cac ttt aaa tct cac tgt gta ctg ctg gga gat gca gct   970
Ser Ser Phe His Phe Lys Ser His Cys Val Leu Leu Gly Asp Ala Ala
                295                 300                 305

cat gct ata gtg ccg ttt ttt ggg caa gga atg aat gcg ggc ttt gaa   1018
His Ala Ile Val Pro Phe Phe Gly Gln Gly Met Asn Ala Gly Phe Glu
            310                 315                 320

gac tgc ttg gta ttt gat gag tta atg gat aaa ttc agt aac gac ctt   1066
Asp Cys Leu Val Phe Asp Glu Leu Met Asp Lys Phe Ser Asn Asp Leu
        325                 330                 335

agt ttg tgt ctt cct gtg ttc tca aga ttg aga atc cca gat gat cac   1114
Ser Leu Cys Leu Pro Val Phe Ser Arg Leu Arg Ile Pro Asp Asp His
    340                 345                 350

gcg att tca gac cta tcc atg tac aat tac ata gag atg cga gca cat   1162
Ala Ile Ser Asp Leu Ser Met Tyr Asn Tyr Ile Glu Met Arg Ala His
355                 360                 365                 370

gtc aac tca agc tgg ttc att ttt cag aag aac atg gag aga ttt ctt   1210
Val Asn Ser Ser Trp Phe Ile Phe Gln Lys Asn Met Glu Arg Phe Leu
                375                 380                 385

cat gcg att atg cca tcg acc ttt atc cct ctc tat aca atg gtc act   1258
His Ala Ile Met Pro Ser Thr Phe Ile Pro Leu Tyr Thr Met Val Thr
            390                 395                 400

ttt tcc aga ata aga tac cat gag gct gtg cag cgt tgg cat tgg caa   1306
Phe Ser Arg Ile Arg Tyr His Glu Ala Val Gln Arg Trp His Trp Gln
        405                 410                 415

aaa aag gtg ata aac aaa gga ctc ttt ttc ttg gga tca ctg ata gcc   1354
Lys Lys Val Ile Asn Lys Gly Leu Phe Phe Leu Gly Ser Leu Ile Ala
    420                 425                 430
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atc agc agt acc tac cta ctt ata cac tac atg tca cca cga tct ttc   1402
Ile Ser Ser Thr Tyr Leu Leu Ile His Tyr Met Ser Pro Arg Ser Phe
435                 440                 445                 450

ctc tgc ttg aga aga cca tgg aac tgg ata gct cac ttc cgg aat aca   1450
Leu Cys Leu Arg Arg Pro Trp Asn Trp Ile Ala His Phe Arg Asn Thr
                455                 460                 465

aca tgt ttc ccc gca aag gcc gtg gac tcc cta gaa caa att tcc aat   1498
Thr Cys Phe Pro Ala Lys Ala Val Asp Ser Leu Glu Gln Ile Ser Asn
            470                 475                 480

ctc att agc agg tga tagaaaggtt ttgtggtagc aaatgcatga tttctctgtg   1553
Leu Ile Ser Arg  *
        485

accaaaatta agcatgaaaa aaatgtttcc attgccatat ttgattcact agtggaagat 1613
agtgttctgc ttataattaa actgaatgta gagtatctct gtatgttaat tgcaattact 1673
ggttgggggg tgcattttaa aagatgaaac atgcagcttc cctacattac acacactcag 1733
gttgagtcat tctaactata aaagtgcaat gactaagatc cttcacttct ctgaaagtaa 1793
ggccctagat gcctcaggga agacagtaat catgcctttt ctttaaaaga cacaatagga 1853
ctcgcaacag cattgactca acacctagga ctaaaaatca caacttaact agcatgttaa 1913
ctgcactttt cattacgtga atggaactta cctaaccaca gggctcagac ttactagata 1973
aaaccagaaa tggaaataag gaattc                                      1999

<210> 32
<211> 486
<212> PRT
<213> Homo sapiens

<400> 32
Met Asp Ser Ser Val Ile Gln Arg Lys Lys Val Ala Val Ile Gly Gly
 1               5                  10                  15
Gly Leu Val Gly Ser Leu Gln Ala Cys Phe Leu Ala Lys Arg Asn Phe
            20                  25                  30
Gln Ile Asp Val Tyr Glu Ala Arg Glu Asp Thr Arg Val Ala Thr Phe
        35                  40                  45
Thr Arg Gly Arg Ser Ile Asn Leu Ala Leu Ser His Arg Gly Arg Gln
    50                  55                  60
Ala Leu Lys Ala Val Gly Leu Glu Asp Gln Ile Val Ser Gln Gly Ile
65                  70                  75                  80
Pro Met Arg Ala Arg Met Ile His Ser Leu Ser Gly Lys Lys Ser Ala
                85                  90                  95
Ile Pro Tyr Gly Thr Lys Ser Gln Tyr Ile Leu Ser Val Ser Arg Glu
            100                 105                 110
Asn Leu Asn Lys Asp Leu Leu Thr Ala Ala Glu Lys Tyr Pro Asn Val
        115                 120                 125
Lys Met His Phe Asn His Arg Leu Leu Lys Cys Asn Pro Glu Glu Gly
    130                 135                 140
Met Ile Thr Val Leu Gly Ser Asp Lys Val Pro Lys Asp Val Thr Cys
145                 150                 155                 160
Asp Leu Ile Val Gly Cys Asp Gly Ala Tyr Ser Thr Val Arg Ser His
                165                 170                 175
Leu Met Lys Lys Pro Arg Phe Asp Tyr Ser Gln Gln Tyr Ile Pro His
            180                 185                 190
Gly Tyr Met Glu Leu Thr Ile Pro Pro Lys Asn Gly Asp Tyr Ala Met
        195                 200                 205
Glu Pro Asn Tyr Leu His Ile Trp Pro Arg Asn Thr Phe Met Met Ile
    210                 215                 220
Ala Leu Pro Asn Met Asn Lys Ser Phe Thr Cys Thr Leu Phe Met Pro
```

```
225                 230                 235                 240
Phe Glu Glu Phe Glu Lys Leu Leu Thr Ser Asn Asp Val Val Asp Phe
                245                 250                 255
Phe Gln Lys Tyr Phe Pro Asp Ala Ile Pro Leu Ile Gly Glu Lys Leu
            260                 265                 270
Leu Val Gln Asp Phe Phe Leu Leu Pro Ala Gln Pro Met Ile Ser Val
        275                 280                 285
Lys Cys Ser Ser Phe His Phe Lys Ser His Cys Val Leu Leu Gly Asp
    290                 295                 300
Ala Ala His Ala Ile Val Pro Phe Phe Gly Gln Gly Met Asn Ala Gly
305                 310                 315                 320
Phe Glu Asp Cys Leu Val Phe Asp Glu Leu Met Asp Lys Phe Ser Asn
                325                 330                 335
Asp Leu Ser Leu Cys Leu Pro Val Phe Ser Arg Leu Arg Ile Pro Asp
            340                 345                 350
Asp His Ala Ile Ser Asp Leu Ser Met Tyr Asn Tyr Ile Glu Met Arg
        355                 360                 365
Ala His Val Asn Ser Ser Trp Phe Ile Phe Gln Lys Asn Met Glu Arg
    370                 375                 380
Phe Leu His Ala Ile Met Pro Ser Thr Phe Ile Pro Leu Tyr Thr Met
385                 390                 395                 400
Val Thr Phe Ser Arg Ile Arg Tyr His Glu Ala Val Gln Arg Trp His
                405                 410                 415
Trp Gln Lys Lys Val Ile Asn Lys Gly Leu Phe Phe Leu Gly Ser Leu
            420                 425                 430
Ile Ala Ile Ser Ser Thr Tyr Leu Leu Ile His Tyr Met Ser Pro Arg
        435                 440                 445
Ser Phe Leu Cys Leu Arg Arg Pro Trp Asn Trp Ile Ala His Phe Arg
    450                 455                 460
Asn Thr Thr Cys Phe Pro Ala Lys Ala Val Asp Ser Leu Glu Gln Ile
465                 470                 475                 480
Ser Asn Leu Ile Ser Arg
                485
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<210> 33
<211> 5415
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (173)...(3739)

<400> 33

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gggcgcagag gaggaaaggg agcaggcgca gggggactgg aaaggcagca tgcgctcgcc 60
aggagcaacc tcggcgccca gggtctgagg ctgcagccca gttcgccatt gtgagccgcc 120
gccgggggag tccgctagcg cacgcgtgcc cccgagtccc cgtccgcgca cg atg ggg 178
                                                          Met Gly
                                                           1

cac ctg ccc acg ggg ata cac ggc gcc cgc cgc ctc ctg cct ctg ctc   226
His Leu Pro Thr Gly Ile His Gly Ala Arg Arg Leu Leu Pro Leu Leu
 5                  10                  15

tgg ctc ttt gtg ctg ttc aag aat gct aca gct ttc cat gta act gtc   274
Trp Leu Phe Val Leu Phe Lys Asn Ala Thr Ala Phe His Val Thr Val
     20                  25                  30

caa gat gat aat aac atc gtt gtc tca tta gaa gct tca gac gtc atc   322
Gln Asp Asp Asn Asn Ile Val Val Ser Leu Glu Ala Ser Asp Val Ile
```

```
35                  40                  45                  50

agt cca gca tct gtg tat gtt gtg aag ata act ggt gaa tcc aaa aat   370
Ser Pro Ala Ser Val Tyr Val Val Lys Ile Thr Gly Glu Ser Lys Asn
                55                  60                  65

tat ttc ttc gaa ttt gag gaa ttc aac agc act ttg cct cct cct gtt   418
Tyr Phe Phe Glu Phe Glu Glu Phe Asn Ser Thr Leu Pro Pro Pro Val
            70                  75                  80

att ttc aag gcc agt tat cat ggc ctt tat tat ata atc act ctg gta   466
Ile Phe Lys Ala Ser Tyr His Gly Leu Tyr Tyr Ile Ile Thr Leu Val
        85                  90                  95

gtg gta aat gga aat gtg gtg acc aag cca tcc aga tca atc act gtg   514
Val Val Asn Gly Asn Val Val Thr Lys Pro Ser Arg Ser Ile Thr Val
    100                 105                 110

tta aca aaa cct cta cct gta acc agt gtt tcc ata tat gac tat aaa   562
Leu Thr Lys Pro Leu Pro Val Thr Ser Val Ser Ile Tyr Asp Tyr Lys
115                 120                 125                 130

cct tct cct gaa aca gga gtc ctg ttt gaa ata cat tat cca gaa aaa   610
Pro Ser Pro Glu Thr Gly Val Leu Phe Glu Ile His Tyr Pro Glu Lys
                135                 140                 145

tat aac gtt ttc aca aga gtg aac att agc tac tgg gaa ggt aaa gac   658
Tyr Asn Val Phe Thr Arg Val Asn Ile Ser Tyr Trp Glu Gly Lys Asp
            150                 155                 160

ttc cgg aca atg cta tat aaa gat ttc ttt aag gga aaa aca gta ttt   706
Phe Arg Thr Met Leu Tyr Lys Asp Phe Phe Lys Gly Lys Thr Val Phe
        165                 170                 175

aat cac tgg ctg cca gga atg tgt tat agt aat atc acc ttt cag ctg   754
Asn His Trp Leu Pro Gly Met Cys Tyr Ser Asn Ile Thr Phe Gln Leu
    180                 185                 190

gta tct gag gca act ttt aat aaa agt acc ctt gtt gag tac agt ggt   802
Val Ser Glu Ala Thr Phe Asn Lys Ser Thr Leu Val Glu Tyr Ser Gly
195                 200                 205                 210

gtc agt cac gaa ccc aaa cag cac aga act gcc cct tat cca cct caa   850
Val Ser His Glu Pro Lys Gln His Arg Thr Ala Pro Tyr Pro Pro Gln
                215                 220                 225

aat att tcc gtt cgt atc gta aac ttg aac aaa aac aac tgg gaa gaa   898
Asn Ile Ser Val Arg Ile Val Asn Leu Asn Lys Asn Asn Trp Glu Glu
            230                 235                 240

cag agt ggc aat ttc cca gaa gaa tcc ttc atg aga tca caa gat aca   946
Gln Ser Gly Asn Phe Pro Glu Glu Ser Phe Met Arg Ser Gln Asp Thr
        245                 250                 255

ata gga aaa gaa aaa ctc ttc cat ttt aca gaa gaa acc cct gaa att   994
Ile Gly Lys Glu Lys Leu Phe His Phe Thr Glu Glu Thr Pro Glu Ile
    260                 265                 270

ccc tcg ggc aac att tct tcc ggt tgg cct gat ttt aat agc agt gac  1042
Pro Ser Gly Asn Ile Ser Ser Gly Trp Pro Asp Phe Asn Ser Ser Asp
275                 280                 285                 290
```

```
tat gaa act acg tct cag cca tat tgg tgg gac agt gca tct gca gct   1090
Tyr Glu Thr Thr Ser Gln Pro Tyr Trp Trp Asp Ser Ala Ser Ala Ala
                295                 300                 305

cct gaa agt gaa gat gaa ttt gtc agc gta ctt ccc atg gaa tac gaa   1138
Pro Glu Ser Glu Asp Glu Phe Val Ser Val Leu Pro Met Glu Tyr Glu
            310                 315                 320

aat aac agt aca ctc agt gag aca gag aag tca aca tca ggc tct ttc   1186
Asn Asn Ser Thr Leu Ser Glu Thr Glu Lys Ser Thr Ser Gly Ser Phe
        325                 330                 335

tcc ttt ttc cct gtg caa atg ata ttg acc tgg tta cca ccc aaa cca   1234
Ser Phe Phe Pro Val Gln Met Ile Leu Thr Trp Leu Pro Pro Lys Pro
    340                 345                 350

ccc act gct ttt gat ggg ttc cat atc cat att gaa cga gaa gag aac   1282
Pro Thr Ala Phe Asp Gly Phe His Ile His Ile Glu Arg Glu Glu Asn
355                 360                 365                 370

ttt act gaa tat ttg atg gtg gat gaa gaa gca cat gaa ttt gtt gca   1330
Phe Thr Glu Tyr Leu Met Val Asp Glu Glu Ala His Glu Phe Val Ala
                375                 380                 385

gaa ctg aag gaa cct ggg aaa tat aag tta tct gtg aca acc ttt agt   1378
Glu Leu Lys Glu Pro Gly Lys Tyr Lys Leu Ser Val Thr Thr Phe Ser
            390                 395                 400

tcc tca gga tct tgt gaa act cga aaa agt cag tca gca aaa tca ctc   1426
Ser Ser Gly Ser Cys Glu Thr Arg Lys Ser Gln Ser Ala Lys Ser Leu
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agc ttt tat atc agt cct tca gga gag tgg att gaa gaa ctg acc gag   1474
Ser Phe Tyr Ile Ser Pro Ser Gly Glu Trp Ile Glu Glu Leu Thr Glu
    420                 425                 430

aag ccg cag cac gtg agt gtc cac gtt tta agc tca acc act gcc ttg   1522
Lys Pro Gln His Val Ser Val His Val Leu Ser Ser Thr Thr Ala Leu
435                 440                 445                 450

atg tcc tgg aca tct tcc caa gag aac tac aac agc acc att gtg tct   1570
Met Ser Trp Thr Ser Ser Gln Glu Asn Tyr Asn Ser Thr Ile Val Ser
                455                 460                 465

gtg gtg tcg ctg acc tgc cag aaa caa aag gag agc cag agg ctt gaa   1618
Val Val Ser Leu Thr Cys Gln Lys Gln Lys Glu Ser Gln Arg Leu Glu
            470                 475                 480

aag cag tac tgc act cag gtg aac tca agc aaa cct att att gaa aat   1666
Lys Gln Tyr Cys Thr Gln Val Asn Ser Ser Lys Pro Ile Ile Glu Asn
        485                 490                 495

ctg gtt cct ggt gcc cag tac cag gtt gta ata tac cta agg aaa ggc   1714
Leu Val Pro Gly Ala Gln Tyr Gln Val Val Ile Tyr Leu Arg Lys Gly
    500                 505                 510

cct ttg att gga cca cct tca gat cct gtg aca ttt gct att gtt ccc   1762
Pro Leu Ile Gly Pro Pro Ser Asp Pro Val Thr Phe Ala Ile Val Pro
515                 520                 525                 530
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aca gga ata aag gat tta atg ctc tat cct ttg ggt cct acg gcc gtg   1810
Thr Gly Ile Lys Asp Leu Met Leu Tyr Pro Leu Gly Pro Thr Ala Val
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gtt ctg agc tgg acc aga cct tat tta ggc gtg ttc aga aaa tac gtg   1858
Val Leu Ser Trp Thr Arg Pro Tyr Leu Gly Val Phe Arg Lys Tyr Val
            550                 555                 560

gtt gaa atg ttt tat ttc aac cct gct aca atg aca tca gag tgg acc   1906
Val Glu Met Phe Tyr Phe Asn Pro Ala Thr Met Thr Ser Glu Trp Thr
        565                 570                 575

acc tac tat gaa ata gca gca act gtt tcc tta act gca tcc gtg aga   1954
Thr Tyr Tyr Glu Ile Ala Ala Thr Val Ser Leu Thr Ala Ser Val Arg
    580                 585                 590

ata gct aat ctg ctg cca gca tgg tac tac aac ttc cgg gtt acc atg   2002
Ile Ala Asn Leu Leu Pro Ala Trp Tyr Tyr Asn Phe Arg Val Thr Met
595                 600                 605                 610

gtg acg tgg gga gat cca gaa ttg agc tgc tgt gac agc tct acc atc   2050
Val Thr Trp Gly Asp Pro Glu Leu Ser Cys Cys Asp Ser Ser Thr Ile
                615                 620                 625

agc ttc ata aca gcc cca gtg gct ccg gaa atc act tct gtg gaa tat   2098
Ser Phe Ile Thr Ala Pro Val Ala Pro Glu Ile Thr Ser Val Glu Tyr
            630                 635                 640

ttc aac agt ctg tta tat atc agt tgg aca tat ggg gat gat aca acg   2146
Phe Asn Ser Leu Leu Tyr Ile Ser Trp Thr Tyr Gly Asp Asp Thr Thr
        645                 650                 655

gac ttg tcc cat tct aga atg ctt cac tgg atg gtg gtt gca gaa gga   2194
Asp Leu Ser His Ser Arg Met Leu His Trp Met Val Val Ala Glu Gly
    660                 665                 670

aaa aag aaa att aaa aag agt gta aca cgc aat gtc atg act gca att   2242
Lys Lys Lys Ile Lys Lys Ser Val Thr Arg Asn Val Met Thr Ala Ile
675                 680                 685                 690

ctc agc ttg cct cca ggc gac atc tat aac ctc tca gta act gct tgt   2290
Leu Ser Leu Pro Pro Gly Asp Ile Tyr Asn Leu Ser Val Thr Ala Cys
                695                 700                 705

act gaa aga gga agt aat acc tcc atg ctc cgc ctt gtc aag cta gaa   2338
Thr Glu Arg Gly Ser Asn Thr Ser Met Leu Arg Leu Val Lys Leu Glu
            710                 715                 720

cca gct cca ccc aaa tca ctc ttc gca gtg aac aaa acc cag act tca   2386
Pro Ala Pro Pro Lys Ser Leu Phe Ala Val Asn Lys Thr Gln Thr Ser
        725                 730                 735

gtg act ttg ctg tgg gtg gaa gag gga gta gct gat ttc ttt gaa gtt   2434
Val Thr Leu Leu Trp Val Glu Glu Gly Val Ala Asp Phe Phe Glu Val
    740                 745                 750

ttc tgt caa caa gtt ggc tcc agt cag aaa acc aaa ctt cag gaa cca   2482
Phe Cys Gln Gln Val Gly Ser Ser Gln Lys Thr Lys Leu Gln Glu Pro
755                 760                 765                 770

gtt gct gtt tct tcc cat gtc gtg acc atc tcc agc ctt ctt cct gcc   2530
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Val Ala Val Ser Ser His Val Val Thr Ile Ser Ser Leu Leu Pro Ala
                775                 780                 785

act gcc tac aat tgt agt gtc acc agc ttt agc cat gac agc ccc agt   2578
Thr Ala Tyr Asn Cys Ser Val Thr Ser Phe Ser His Asp Ser Pro Ser
            790                 795                 800

gtc cct acg ttc ata gcc gtc tca aca atg gtt aca gag atg aat ccc   2626
Val Pro Thr Phe Ile Ala Val Ser Thr Met Val Thr Glu Met Asn Pro
        805                 810                 815

aat gtg gta gtg atc tcc gtg ctg gcc atc ctt agc aca ctt tta att   2674
Asn Val Val Val Ile Ser Val Leu Ala Ile Leu Ser Thr Leu Leu Ile
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gga ctg ttg ctt gtt acc ctc att att ctt agg aaa aag cat ctg cag   2722
Gly Leu Leu Leu Val Thr Leu Ile Ile Leu Arg Lys Lys His Leu Gln
835                 840                 845                 850

atg gct agg gag tgt gga gct ggt aca ttt gtc aat ttt gca tcc tta   2770
Met Ala Arg Glu Cys Gly Ala Gly Thr Phe Val Asn Phe Ala Ser Leu
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gag agg gat gga aag ctt cca tac aac tgg agt aaa aat ggt tta aag   2818
Glu Arg Asp Gly Lys Leu Pro Tyr Asn Trp Ser Lys Asn Gly Leu Lys
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aag agg aaa ctg aca aac ccg gtt caa ctg gat gac ttt gat gcc tat   2866
Lys Arg Lys Leu Thr Asn Pro Val Gln Leu Asp Asp Phe Asp Ala Tyr
        885                 890                 895

att aag gat atg gcc aaa gac tct gac tat aaa ttt tct ctt cag ttt   2914
Ile Lys Asp Met Ala Lys Asp Ser Asp Tyr Lys Phe Ser Leu Gln Phe
    900                 905                 910

gag gag ttg aaa ttg att gga ctg gat atc cca cac ttt gct gca gat   2962
Glu Glu Leu Lys Leu Ile Gly Leu Asp Ile Pro His Phe Ala Ala Asp
915                 920                 925                 930

ctt cca ctg aat cga tgt aaa aac cgt tac aca aac atc cta cca tat   3010
Leu Pro Leu Asn Arg Cys Lys Asn Arg Tyr Thr Asn Ile Leu Pro Tyr
                935                 940                 945

gac ttc agc cgt gtg aga tta gtc tcc atg aat gaa gag gaa ggt gca   3058
Asp Phe Ser Arg Val Arg Leu Val Ser Met Asn Glu Glu Glu Gly Ala
            950                 955                 960

gac tac atc aat gcc aac tat att cct gga tac aac tca ccc cag gag   3106
Asp Tyr Ile Asn Ala Asn Tyr Ile Pro Gly Tyr Asn Ser Pro Gln Glu
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tat att gcc acc cag ggg cca ctg cct gaa acc aga aat gac ttc tgg   3154
Tyr Ile Ala Thr Gln Gly Pro Leu Pro Glu Thr Arg Asn Asp Phe Trp
    980                 985                 990

aag atg gtc ctg caa caa aag tct cag att att gtc atg ctc act cag   3202
Lys Met Val Leu Gln Gln Lys Ser Gln Ile Ile Val Met Leu Thr Gln
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tgt aat gag aaa agg agg gtg aaa tgt gac cat tac tgg cca ttc acg   3250
Cys Asn Glu Lys Arg Arg Val Lys Cys Asp His Tyr Trp Pro Phe Thr
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                1015                1020                1025

gaa gaa cct ata gcc tat gga gac atc act gtg gag atg att tca gag   3298
Glu Glu Pro Ile Ala Tyr Gly Asp Ile Thr Val Glu Met Ile Ser Glu
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gaa gag cag gac gac tgg gcc tgt aga cac ttc cgg atc aac tat gct   3346
Glu Glu Gln Asp Asp Trp Ala Cys Arg His Phe Arg Ile Asn Tyr Ala
        1045                1050                1055

gac gag atg cag gat gtg atg cat ttt aac tac act gca tgg cct gat   3394
Asp Glu Met Gln Asp Val Met His Phe Asn Tyr Thr Ala Trp Pro Asp
    1060                1065                1070

cat ggt gtg ccc aca gca aat gct gca gaa agt atc ctg cag ttt gta   3442
His Gly Val Pro Thr Ala Asn Ala Ala Glu Ser Ile Leu Gln Phe Val
1075                1080                1085                1090

cac atg gtc cga cag caa gct acc aag agc aaa ggt ccc atg atc att   3490
His Met Val Arg Gln Gln Ala Thr Lys Ser Lys Gly Pro Met Ile Ile
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cac tgc agt gct ggc gtg gga cgg aca gga aca ttc att gcc ctg gac   3538
His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala Leu Asp
            1110                1115                1120

agg ctc ttg cag cac att cgg gat cat gag ttt gtt gac atc tta ggg   3586
Arg Leu Leu Gln His Ile Arg Asp His Glu Phe Val Asp Ile Leu Gly
        1125                1130                1135

ctg gtg tca gaa atg agg tca tac cgg atg tct atg gta cag aca gag   3634
Leu Val Ser Glu Met Arg Ser Tyr Arg Met Ser Met Val Gln Thr Glu
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gag cag tac att ttt atc cat cag tgt gtg caa ctg atg tgg atg aag   3682
Glu Gln Tyr Ile Phe Ile His Gln Cys Val Gln Leu Met Trp Met Lys
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aag aag cag cag ttc tgc atc agt gat gtc ata tac gag aat gtt agc   3730
Lys Lys Gln Gln Phe Cys Ile Ser Asp Val Ile Tyr Glu Asn Val Ser
                1175                1180                1185

aag tcc tag ttcagaatcc ggagcagaga ggacatgatg tgcgcccatc           3779
Lys Ser  *

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Thr Val Gln Asp Asp Asn Asn Ile Val Val Ser Leu Glu Ala Ser Asp
35 40 45
Val Ile Ser Pro Ala Ser Val Tyr Val Val Lys Ile Thr Gly Glu Ser
50 55 60
Lys Asn Tyr Phe Phe Glu Phe Glu Glu Phe Asn Ser Thr Leu Pro Pro
65 70 75 80
Pro Val Ile Phe Lys Ala Ser Tyr His Gly Leu Tyr Tyr Ile Ile Thr
85 90 95
Leu Val Val Val Asn Gly Asn Val Val Thr Lys Pro Ser Arg Ser Ile
100 105 110
Thr Val Leu Thr Lys Pro Leu Pro Val Thr Ser Val Ser Ile Tyr Asp
115 120 125
Tyr Lys Pro Ser Pro Glu Thr Gly Val Leu Phe Glu Ile His Tyr Pro
130 135 140
Glu Lys Tyr Asn Val Phe Thr Arg Val Asn Ile Ser Tyr Trp Glu Gly
145 150 155 160
Lys Asp Phe Arg Thr Met Leu Tyr Lys Asp Phe Phe Lys Gly Lys Thr
165 170 175
Val Phe Asn His Trp Leu Pro Gly Met Cys Tyr Ser Asn Ile Thr Phe
180 185 190
Gln Leu Val Ser Glu Ala Thr Phe Asn Lys Ser Thr Leu Val Glu Tyr
195 200 205
Ser Gly Val Ser His Glu Pro Lys Gln His Arg Thr Ala Pro Tyr Pro
210 215 220
Pro Gln Asn Ile Ser Val Arg Ile Val Asn Leu Asn Lys Asn Asn Trp
225 230 235 240
Glu Glu Gln Ser Gly Asn Phe Pro Glu Glu Ser Phe Met Arg Ser Gln
245 250 255
Asp Thr Ile Gly Lys Glu Lys Leu Phe His Phe Thr Glu Glu Thr Pro
260 265 270
Glu Ile Pro Ser Gly Asn Ile Ser Ser Gly Trp Pro Asp Phe Asn Ser
275 280 285
Ser Asp Tyr Glu Thr Thr Ser Gln Pro Tyr Trp Trp Asp Ser Ala Ser
290 295 300
Ala Ala Pro Glu Ser Glu Asp Glu Phe Val Ser Val Leu Pro Met Glu
305 310 315 320
Tyr Glu Asn Asn Ser Thr Leu Ser Glu Thr Glu Lys Ser Thr Ser Gly

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Ser Phe Ser Phe Phe Pro Val Gln Met Ile Leu Thr Trp Leu Pro Pro
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Lys Pro Pro Thr Ala Phe Asp Gly Phe His Ile His Ile Glu Arg Glu
        355                 360                 365
Glu Asn Phe Thr Glu Tyr Leu Met Val Asp Glu Glu Ala His Glu Phe
    370                 375                 380
Val Ala Glu Leu Lys Glu Pro Gly Lys Tyr Lys Leu Ser Val Thr Thr
385                 390                 395                 400
Phe Ser Ser Ser Gly Ser Cys Glu Thr Arg Lys Ser Gln Ser Ala Lys
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Ser Leu Ser Phe Tyr Ile Ser Pro Ser Gly Glu Trp Ile Glu Glu Leu
            420                 425                 430
Thr Glu Lys Pro Gln His Val Ser Val His Val Leu Ser Ser Thr Thr
        435                 440                 445
Ala Leu Met Ser Trp Thr Ser Ser Gln Glu Asn Tyr Asn Ser Thr Ile
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Val Ser Val Val Ser Leu Thr Cys Gln Lys Gln Lys Glu Ser Gln Arg
465                 470                 475                 480
Leu Glu Lys Gln Tyr Cys Thr Gln Val Asn Ser Ser Lys Pro Ile Ile
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Glu Asn Leu Val Pro Gly Ala Gln Tyr Gln Val Val Ile Tyr Leu Arg
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Lys Gly Pro Leu Ile Gly Pro Pro Ser Asp Pro Val Thr Phe Ala Ile
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Val Pro Thr Gly Ile Lys Asp Leu Met Leu Tyr Pro Leu Gly Pro Thr
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Ala Val Val Leu Ser Trp Thr Arg Pro Tyr Leu Gly Val Phe Arg Lys
545                 550                 555                 560
Tyr Val Val Glu Met Phe Tyr Phe Asn Pro Ala Thr Met Thr Ser Glu
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Trp Thr Thr Tyr Tyr Glu Ile Ala Ala Thr Val Ser Leu Thr Ala Ser
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Val Arg Ile Ala Asn Leu Leu Pro Ala Trp Tyr Tyr Asn Phe Arg Val
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Thr Met Val Thr Trp Gly Asp Pro Glu Leu Ser Cys Cys Asp Ser Ser
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Thr Ile Ser Phe Ile Thr Ala Pro Val Ala Pro Glu Ile Thr Ser Val
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Glu Tyr Phe Asn Ser Leu Leu Tyr Ile Ser Trp Thr Tyr Gly Asp Asp
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Thr Thr Asp Leu Ser His Ser Arg Met Leu His Trp Met Val Val Ala
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Glu Gly Lys Lys Lys Ile Lys Lys Ser Val Thr Arg Asn Val Met Thr
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Ala Ile Leu Ser Leu Pro Pro Gly Asp Ile Tyr Asn Leu Ser Val Thr
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Ala Cys Thr Glu Arg Gly Ser Asn Thr Ser Met Leu Arg Leu Val Lys
705                 710                 715                 720
Leu Glu Pro Ala Pro Pro Lys Ser Leu Phe Ala Val Asn Lys Thr Gln
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Thr Ser Val Thr Leu Leu Trp Val Glu Glu Gly Val Ala Asp Phe Phe
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Glu Val Phe Cys Gln Gln Val Gly Ser Ser Gln Lys Thr Lys Leu Gln
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Glu Pro Val Ala Val Ser Ser His Val Val Thr Ile Ser Ser Leu Leu
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Pro Ala Thr Ala Tyr Asn Cys Ser Val Thr Ser Phe Ser His Asp Ser
785                 790                 795                 800
Pro Ser Val Pro Thr Phe Ile Ala Val Ser Thr Met Val Thr Glu Met
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Leu Gln Met Ala Arg Glu Cys Gly Ala Gly Thr Phe Val Asn Phe Ala
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Ser Leu Glu Arg Asp Gly Lys Leu Pro Tyr Asn Trp Ser Lys Asn Gly
865                 870                 875                 880
Leu Lys Lys Arg Lys Leu Thr Asn Pro Val Gln Leu Asp Asp Phe Asp
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Ala Tyr Ile Lys Asp Met Ala Lys Asp Ser Asp Tyr Lys Phe Ser Leu
            900                 905                 910
Gln Phe Glu Glu Leu Lys Leu Ile Gly Leu Asp Ile Pro His Phe Ala
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Ala Asp Leu Pro Leu Asn Arg Cys Lys Asn Arg Tyr Thr Asn Ile Leu
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Pro Tyr Asp Phe Ser Arg Val Arg Leu Val Ser Met Asn Glu Glu Glu
945                 950                 955                 960
Gly Ala Asp Tyr Ile Asn Ala Asn Tyr Ile Pro Gly Tyr Asn Ser Pro
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Gln Glu Tyr Ile Ala Thr Gln Gly Pro Leu Pro Glu Thr Arg Asn Asp
            980                 985                 990
Phe Trp Lys Met Val Leu Gln Gln Lys Ser Gln Ile Ile Val Met Leu
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Thr Gln Cys Asn Glu Lys Arg Arg Val Lys Cys Asp His Tyr Trp Pro
    1010                1015                1020
Phe Thr Glu Glu Pro Ile Ala Tyr Gly Asp Ile Thr Val Glu Met Ile
1025                1030                1035                1040
Ser Glu Glu Glu Gln Asp Asp Trp Ala Cys Arg His Phe Arg Ile Asn
                1045                1050                1055
Tyr Ala Asp Glu Met Gln Asp Val Met His Phe Asn Tyr Thr Ala Trp
            1060                1065                1070
Pro Asp His Gly Val Pro Thr Ala Asn Ala Ala Glu Ser Ile Leu Gln
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Phe Val His Met Val Arg Gln Gln Ala Thr Lys Ser Lys Gly Pro Met
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Ile Ile His Cys Ser Ala Gly Val Gly Arg Thr Gly Thr Phe Ile Ala
1105                1110                1115                1120
Leu Asp Arg Leu Leu Gln His Ile Arg Asp His Glu Phe Val Asp Ile
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Leu Gly Leu Val Ser Glu Met Arg Ser Tyr Arg Met Ser Met Val Gln
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Thr Glu Glu Gln Tyr Ile Phe Ile His Gln Cys Val Gln Leu Met Trp
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tgc tgc ttt gct gcc ccc aga cag cgc cag tcc acc ctt gtg ctc ttc   98
Cys Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe
            20                  25                  30

cct gga gac ctg aga acc aat ctc acc gac agg cag ctg gca gag gaa  146
Pro Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu
        35                  40                  45

tac ctg tac cgc tat ggt tac act cgg gtg gca gag atg cgt gga gag  194
Tyr Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu
    50                  55                  60

tcg aaa tct ctg ggg cct gcg ctg ctg ctt ctc cag aag caa ctg tcc  242
Ser Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser
65                  70                  75

ctg ccc gag acc ggt gag ctg gat agc gcc acg ctg aag gcc atg cga  290
Leu Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg
80                  85                  90                  95

acc cca cgg tgc ggg gtc cca gac ctg ggc aga ttc caa acc ttt gag  338
Thr Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu
            100                 105                 110

ggc gac ctc aag tgg cac cac cac aac atc acc tat tgg atc caa aac  386
Gly Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn
        115                 120                 125

tac tcg gaa gac ttg ccg cgg gcg gtg att gac gac gcc ttt gcc cgc  434
Tyr Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg
    130                 135                 140

gcc ttc gca ctg tgg agc gcg gtg acg ccg ctc acc ttc act cgc gtg  482
Ala Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val
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tac agc cgg gac gca gac atc gtc atc cag ttt ggt gtc gcg gag cac  530
Tyr Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His
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gga gac ggg tat ccc ttc gac ggg aag gac ggg ctc ctg gca cac gcc  578
Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala
            180                 185                 190

ttt cct cct ggc ccc ggc att cag gga gac gcc cat ttc gac gat gac  626
Phe Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp
        195                 200                 205

gag ttg tgg tcc ctg ggc aag ggc gtc gtg gtt cca act cgg ttt gga  674
Glu Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly
    210                 215                 220

aac gca gat ggc gcg gcc tgc cac ttc ccc ttc atc ttc gag ggc cgc  722
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Pro Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro
            275                 280                 285

tgc cag ttt cca ttc atc ttc caa ggc caa tcc tac tcc gcc tgc acc   914
Cys Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr
        290                 295                 300

acg gac ggt cgc tcc gac ggc tac cgc tgg tgc gcc acc acc gcc aac   962
Thr Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn
    305                 310                 315

tac gac cgg gac aag ctc ttc ggc ttc tgc ccg acc cga gct gac tcg   1010
Tyr Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser
320                 325                 330                 335

acg gtg atg ggg ggc aac tcg gcg ggg gag ctg tgc gtc ttc ccc ttc   1058
Thr Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe
                340                 345                 350

act ttc ctg ggt aag gag tac tcg acc tgt acc agc gag ggc cgc gga   1106
Thr Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly
            355                 360                 365

gat ggg cgc ctc tgg tgc gct acc acc tcg aac ttt gac agc gac aag   1154
Asp Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys
        370                 375                 380

aag tgg ggc ttc tgc ccg gac caa gga tac agt ttg ttc ctc gtg gcg   1202
Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala
    385                 390                 395

gcg cat gag ttc ggc cac gcg ctg ggc tta gat cat tcc tca gtg ccg   1250
Ala His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro
400                 405                 410                 415

gag gcg ctc atg tac cct atg tac cgc ttc act gag ggg ccc ccc ttg   1298
Glu Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu
                420                 425                 430

cat aag gac gac gtg aat ggc atc cgg cac ctc tat ggt cct cgc cct   1346
His Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro
            435                 440                 445

gaa cct gag cca cgg cct cca acc acc acc aca ccg cag ccc acg gct   1394
Glu Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala
        450                 455                 460

ccc ccg acg gtc tgc ccc acc gga ccc ccc act gtc cac ccc tca gag   1442
Pro Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu
    465                 470                 475

cgc ccc aca gct ggc ccc aca ggt ccc ccc tca gct ggc ccc aca ggt   1490
Arg Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly
480                 485                 490                 495
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ccc ccc act gct ggc cct tct acg gcc act act gtg cct ttg agt ccg   1538
Pro Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro
                500                 505                 510

gtg gac gat gcc tgc aac gtg aac atc ttc gac gcc atc gcg gag att   1586
Val Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile
            515                 520                 525

ggg aac cag ctg tat ttg ttc aag gat ggg aag tac tgg cga ttc tct   1634
Gly Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser
        530                 535                 540

gag ggc agg ggg agc cgg ccg cag ggc ccc ttc ctt atc gcc gac aag   1682
Glu Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys
    545                 550                 555

tgg ccc gcg ctg ccc cgc aag ctg gac tcg gtc ttt gag gag ccg ctc   1730
Trp Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu
560                 565                 570                 575

tcc aag aag ctt ttc ttc ttc tct ggg cgc cag gtg tgg gtg tac aca   1778
Ser Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr
                580                 585                 590

ggc gcg tcg gtg ctg ggc ccg agg cgt ctg gac aag ctg ggc ctg gga   1826
Gly Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly
            595                 600                 605

gcc gac gtg gcc cag gtg acc ggg gcc ctc cgg agt ggc agg ggg aag   1874
Ala Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys
        610                 615                 620

atg ctg ctg ttc agc ggg cgg cgc ctc tgg agg ttc gac gtg aag gcg   1922
Met Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala
    625                 630                 635

cag atg gtg gat ccc cgg agc gcc agc gag gtg gac cgg atg ttc ccc   1970
Gln Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro
640                 645                 650                 655

ggg gtg cct ttg gac acg cac gac gtc ttc cag tac cga gag aaa gcc   2018
Gly Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala
                660                 665                 670

tat ttc tgc cag gac cgc ttc tac tgg cgc gtg agt tcc cgg agt gag   2066
Tyr Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu
            675                 680                 685

ttg aac cag gtg gac caa gtg ggc tac gtg acc tat gac atc ctg cag   2114
Leu Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln
        690                 695                 700

tgc cct gag gac tag ggctcccgtc ctgctttggc agtgccatgt aaatccccac   2169
Cys Pro Glu Asp  *
    705

tgggaccaac cctggggaag gagccagttt gccggataca aactggtatt ctgttctgga 2229
ggaaagggag gagtggaggt gggctgggcc ctctcttctc acctttgttt tttgttggag 2289
tgtttctaat aaacttggat tctctaacct ttaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2349
```

aaaaaaaaaa aaaaaaaaaa aaaa

<210> 36
<211> 707
<212> PRT
<213> Homo sapiens

<400> 36
Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
1 5 10 15
Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
20 25 30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
35 40 45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
50 55 60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
65 70 75 80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
85 90 95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
100 105 110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
115 120 125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
130 135 140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
145 150 155 160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
165 170 175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
180 185 190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
195 200 205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
210 215 220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
225 230 235 240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
245 250 255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
260 265 270
Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
275 280 285
Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
290 295 300
Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
305 310 315 320
Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
325 330 335
Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
340 345 350
Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
355 360 365
Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
370 375 380
Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
385 390 395 400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
405 410 415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His

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            420                 425                 430
Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
        435                 440                 445
Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
    450                 455                 460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465                 470                 475                 480
Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
                485                 490                 495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
            500                 505                 510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
        515                 520                 525
Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
    530                 535                 540
Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
545                 550                 555                 560
Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
                565                 570                 575
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
            580                 585                 590
Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
        595                 600                 605
Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
    610                 615                 620
Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
625                 630                 635                 640
Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
                645                 650                 655
Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
            660                 665                 670
Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
        675                 680                 685
Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
    690                 695                 700
Pro Glu Asp
705
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<210> 37
<211> 934
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (8)...(751)

<400> 37

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tgagaag atg caa cca atc ctg ctt ctg ctg gcc ttc ctc ctg ctg ccc   49
        Met Gln Pro Ile Leu Leu Leu Leu Ala Phe Leu Leu Leu Pro
         1               5                  10

agg gca gat gca ggg gag atc atc ggg gga cat gag gcc aag ccc cac   97
Arg Ala Asp Ala Gly Glu Ile Ile Gly Gly His Glu Ala Lys Pro His
 15                  20                  25                  30

tcc cgc ccc tac atg gct tat ctt atg atc tgg gat cag aag tct ctg   145
Ser Arg Pro Tyr Met Ala Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu
                35                  40                  45
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aag agg tgc ggt ggc ttc ctg ata caa gac gac ttc gtg ctg aca gct   193
Lys Arg Cys Gly Gly Phe Leu Ile Gln Asp Asp Phe Val Leu Thr Ala
            50                  55                  60

gct cac tgt tgg gga agc tcc ata aat gtc acc ttg ggg gcc cac aat   241
Ala His Cys Trp Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn
        65                  70                  75

atc aaa gaa cag gag ccg acc cag cag ttt atc cct gtg aaa aga ccc   289
Ile Lys Glu Gln Glu Pro Thr Gln Gln Phe Ile Pro Val Lys Arg Pro
    80                  85                  90

atc ccc cat cca gcc tat aat cct aag aac ttc tcc aac gac atc atg   337
Ile Pro His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met
95                  100                 105                 110

cta ctg cag ctg gag aga aag gcc aag cgg acc aga gct gtg cag ccc   385
Leu Leu Gln Leu Glu Arg Lys Ala Lys Arg Thr Arg Ala Val Gln Pro
                115                 120                 125

ctc agg cta cct agc aac aag gcc cag gtg aag cca ggg cag aca tgc   433
Leu Arg Leu Pro Ser Asn Lys Ala Gln Val Lys Pro Gly Gln Thr Cys
            130                 135                 140

agt gtg gcc ggc tgg ggg cag acg gcc ccc ctg gga aaa cac tca cac   481
Ser Val Ala Gly Trp Gly Gln Thr Ala Pro Leu Gly Lys His Ser His
        145                 150                 155

aca cta caa gag gtg aag atg aca gtg cag gaa gat cga aag tgc gaa   529
Thr Leu Gln Glu Val Lys Met Thr Val Gln Glu Asp Arg Lys Cys Glu
    160                 165                 170

tct gac tta cgc cat tat tac gac agt acc att gag ttg tgc gtg ggg   577
Ser Asp Leu Arg His Tyr Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly
175                 180                 185                 190

gac cca gag att aaa aag act tcc ttt aag ggg gac tct gga ggc cct   625
Asp Pro Glu Ile Lys Lys Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro
                195                 200                 205

ctt gtg tgt aac aag gtg gcc cag ggc att gtc tcc tat gga cga aac   673
Leu Val Cys Asn Lys Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn
            210                 215                 220

aat ggc atg cct cca cga gcc tgc acc aaa gtc tca agc ttt gta cac   721
Asn Gly Met Pro Pro Arg Ala Cys Thr Lys Val Ser Ser Phe Val His
        225                 230                 235

tgg ata aag aaa acc atg aaa cgc tac taa ctacaggaag caaactaagc     771
Trp Ile Lys Lys Thr Met Lys Arg Tyr  *
    240                 245

ccccgctgta atgaaacacc ttctctggag ccaagtccag atttacactg ggagaggtgc 831
cagcaactga ataaatacct ctcccagtgt aaatctggag ccaagtccag atttacactg 891
ggagaggtgc cagcaactga ataaatacct cttagctgag tgg                   934

<210> 38
<211> 247
<212> PRT
<213> Homo sapiens
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<400> 38
Met Gln Pro Ile Leu Leu Leu Leu Ala Phe Leu Leu Leu Pro Arg Ala
1 5 10 15
Asp Ala Gly Glu Ile Ile Gly Gly His Glu Ala Lys Pro His Ser Arg
20 25 30
Pro Tyr Met Ala Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu Lys Arg
35 40 45
Cys Gly Gly Phe Leu Ile Gln Asp Asp Phe Val Leu Thr Ala Ala His
50 55 60
Cys Trp Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn Ile Lys
65 70 75 80
Glu Gln Glu Pro Thr Gln Gln Phe Ile Pro Val Lys Arg Pro Ile Pro
85 90 95
His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met Leu Leu
100 105 110
Gln Leu Glu Arg Lys Ala Lys Arg Thr Arg Ala Val Gln Pro Leu Arg
115 120 125
Leu Pro Ser Asn Lys Ala Gln Val Lys Pro Gly Gln Thr Cys Ser Val
130 135 140
Ala Gly Trp Gly Gln Thr Ala Pro Leu Gly Lys His Ser His Thr Leu
145 150 155 160
Gln Glu Val Lys Met Thr Val Gln Glu Asp Arg Lys Cys Glu Ser Asp
165 170 175
Leu Arg His Tyr Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly Asp Pro
180 185 190
Glu Ile Lys Lys Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro Leu Val
195 200 205
Cys Asn Lys Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn Asn Gly
210 215 220
Met Pro Pro Arg Ala Cys Thr Lys Val Ser Ser Phe Val His Trp Ile
225 230 235 240
Lys Lys Thr Met Lys Arg Tyr
245

<210> 39
<211> 1853
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (27)...(1814)

<400> 39
aaaacgcagg gagggaggct gtcacc atg ccg gcc tgc tgc agc tgc agt gat 53
Met Pro Ala Cys Cys Ser Cys Ser Asp
1 5

gtt ttc cag tat gag acg aac aaa gtc act cgg atc cag agc atg aat 101
Val Phe Gln Tyr Glu Thr Asn Lys Val Thr Arg Ile Gln Ser Met Asn
10 15 20 25

tat ggc acc att aag tgg ttc ttc cac gtg atc atc ttt tcc tac gtt 149
Tyr Gly Thr Ile Lys Trp Phe Phe His Val Ile Ile Phe Ser Tyr Val
30 35 40

tgc ttt gct ctg gtg agt gac aag ctg tac cag cgg aaa gag cct gtc 197
Cys Phe Ala Leu Val Ser Asp Lys Leu Tyr Gln Arg Lys Glu Pro Val
45 50 55

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atc agt tct gtg cac acc aag gtg aag ggg ata gca gag gtg aaa gag   245
Ile Ser Ser Val His Thr Lys Val Lys Gly Ile Ala Glu Val Lys Glu
         60                  65                  70

gag atc gtg gag aat gga gtg aag aag ttg gtg cac agt gtc ttt gac   293
Glu Ile Val Glu Asn Gly Val Lys Lys Leu Val His Ser Val Phe Asp
     75                  80                  85

acc gca gac tac acc ttc cct ttg cag ggg aac tct ttc ttc gtg atg   341
Thr Ala Asp Tyr Thr Phe Pro Leu Gln Gly Asn Ser Phe Phe Val Met
 90                  95                 100                 105

aca aac ttt ctc aaa aca gaa ggc caa gag cag cgg ttg tgt ccc gag   389
Thr Asn Phe Leu Lys Thr Glu Gly Gln Glu Gln Arg Leu Cys Pro Glu
                110                 115                 120

tat ccc acc cgc agg acg ctc tgt tcc tct gac cga ggt tgt aaa aag   437
Tyr Pro Thr Arg Arg Thr Leu Cys Ser Ser Asp Arg Gly Cys Lys Lys
            125                 130                 135

gga tgg atg gac ccg cag agc aaa gga att cag acc gga agg tgt gta   485
Gly Trp Met Asp Pro Gln Ser Lys Gly Ile Gln Thr Gly Arg Cys Val
        140                 145                 150

gtg cat gaa ggg aac cag aag acc tgt gaa gtc tct gcc tgg tgc ccc   533
Val His Glu Gly Asn Gln Lys Thr Cys Glu Val Ser Ala Trp Cys Pro
    155                 160                 165

atc gag gca gtg gaa gag gcc ccc cgg cct gct ctc ttg aac agt gcc   581
Ile Glu Ala Val Glu Glu Ala Pro Arg Pro Ala Leu Leu Asn Ser Ala
170                 175                 180                 185

gaa aac ttc act gtg ctc atc aag aac aat atc gac ttc ccc ggc cac   629
Glu Asn Phe Thr Val Leu Ile Lys Asn Asn Ile Asp Phe Pro Gly His
                190                 195                 200

aac tac acc acg aga aac atc ctg cca ggt tta aac atc act tgt acc   677
Asn Tyr Thr Thr Arg Asn Ile Leu Pro Gly Leu Asn Ile Thr Cys Thr
            205                 210                 215

ttc cac aag act cag aat cca cag tgt ccc att ttc cga cta gga gac   725
Phe His Lys Thr Gln Asn Pro Gln Cys Pro Ile Phe Arg Leu Gly Asp
        220                 225                 230

atc ttc cga gaa aca ggc gat aat ttt tca gat gtg gca att cag ggc   773
Ile Phe Arg Glu Thr Gly Asp Asn Phe Ser Asp Val Ala Ile Gln Gly
    235                 240                 245

gga ata atg ggc att gag atc tac tgg gac tgc aac cta gac cgt tgg   821
Gly Ile Met Gly Ile Glu Ile Tyr Trp Asp Cys Asn Leu Asp Arg Trp
250                 255                 260                 265

ttc cat cac tgc cat ccc aaa tac agt ttc cgt cgc ctt gac gac aag   869
Phe His His Cys His Pro Lys Tyr Ser Phe Arg Arg Leu Asp Asp Lys
                270                 275                 280

acc acc aac gtg tcc ttg tac cct ggc tac aac ttc aga tac gcc aag   917
Thr Thr Asn Val Ser Leu Tyr Pro Gly Tyr Asn Phe Arg Tyr Ala Lys
            285                 290                 295

tac tac aag gaa aac aat gtt gag aaa cgg act ctg ata aaa gtc ttc   965
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Tyr Tyr Lys Glu Asn Asn Val Glu Lys Arg Thr Leu Ile Lys Val Phe
        300                 305                 310

ggg atc cgt ttt gac atc ctg gtt ttt ggc acc gga gga aaa ttt gac   1013
Gly Ile Arg Phe Asp Ile Leu Val Phe Gly Thr Gly Gly Lys Phe Asp
    315                 320                 325

att atc cag ctg gtt gtg tac atc ggc tca acc ctc tcc tac ttc ggt   1061
Ile Ile Gln Leu Val Val Tyr Ile Gly Ser Thr Leu Ser Tyr Phe Gly
330                 335                 340                 345

ctg gcc gct gtg ttc atc gac ttc ctc atc gac act tac tcc agt aac   1109
Leu Ala Ala Val Phe Ile Asp Phe Leu Ile Asp Thr Tyr Ser Ser Asn
                350                 355                 360

tgc tgt cgc tcc cat att tat ccc tgg tgc aag tgc tgt cag ccc tgt   1157
Cys Cys Arg Ser His Ile Tyr Pro Trp Cys Lys Cys Cys Gln Pro Cys
            365                 370                 375

gtg gtc aac gaa tac tac tac agg aag aag tgc gag tcc att gtg gag   1205
Val Val Asn Glu Tyr Tyr Tyr Arg Lys Lys Cys Glu Ser Ile Val Glu
        380                 385                 390

cca aag ccg aca tta aag tat gtg tcc ttt gtg gat gaa tcc cac att   1253
Pro Lys Pro Thr Leu Lys Tyr Val Ser Phe Val Asp Glu Ser His Ile
    395                 400                 405

agg atg gtg aac cag cag cta cta ggg aga agt ctg caa gat gtc aag   1301
Arg Met Val Asn Gln Gln Leu Leu Gly Arg Ser Leu Gln Asp Val Lys
410                 415                 420                 425

ggc caa gaa gtc cca aga cct gcg atg gac ttc aca gat ttg tcc agg   1349
Gly Gln Glu Val Pro Arg Pro Ala Met Asp Phe Thr Asp Leu Ser Arg
                430                 435                 440

ctg ccc ctg gcc ctc cat gac aca ccc ccg att cct gga caa cca gag   1397
Leu Pro Leu Ala Leu His Asp Thr Pro Pro Ile Pro Gly Gln Pro Glu
            445                 450                 455

gag ata cag ctg ctt aga aag gag gcg act cct aga tcc agg gat agc   1445
Glu Ile Gln Leu Leu Arg Lys Glu Ala Thr Pro Arg Ser Arg Asp Ser
        460                 465                 470

ccc gtc tgg tgc cag tgt gga agc tgc ctc cca tct caa ctc cct gag   1493
Pro Val Trp Cys Gln Cys Gly Ser Cys Leu Pro Ser Gln Leu Pro Glu
    475                 480                 485

agc cac agg tgc ctg gag gag ctg tgc tgc cgg aaa aag ccg ggg gcc   1541
Ser His Arg Cys Leu Glu Glu Leu Cys Cys Arg Lys Lys Pro Gly Ala
490                 495                 500                 505

tgc atc acc acc tca gag ctg ttc agg aag ctg gtc ctg tcc aga cac   1589
Cys Ile Thr Thr Ser Glu Leu Phe Arg Lys Leu Val Leu Ser Arg His
                510                 515                 520

gtc ctg cag ttc ctc ctg ctc tac cag gag ccc ttg ctg gcg ctg gat   1637
Val Leu Gln Phe Leu Leu Leu Tyr Gln Glu Pro Leu Leu Ala Leu Asp
            525                 530                 535

gtg gat tcc acc aac agc cgg ctg cgg cac tgt gcc tac agg tgc tac   1685
Val Asp Ser Thr Asn Ser Arg Leu Arg His Cys Ala Tyr Arg Cys Tyr
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      540                 545                 550

gcc acc tgg cgc ttc ggc tcc cag gac atg gct gac ttt gcc atc ctg   1733
Ala Thr Trp Arg Phe Gly Ser Gln Asp Met Ala Asp Phe Ala Ile Leu
    555                 560                 565

ccc agc tgc tgc cgc tgg agg atc cgg aaa gag ttt ccg aag agt gaa   1781
Pro Ser Cys Cys Arg Trp Arg Ile Arg Lys Glu Phe Pro Lys Ser Glu
570                 575                 580                 585

ggg cag tac agt ggc ttc aag agt cct tac tga agccaggcac cgtggctcac 1834
Gly Gln Tyr Ser Gly Phe Lys Ser Pro Tyr  *
                590                 595

gtctgtaatc ccacctttt                                              1853

<210> 40
<211> 595
<212> PRT
<213> Homo sapiens

<400> 40
Met Pro Ala Cys Cys Ser Cys Ser Asp Val Phe Gln Tyr Glu Thr Asn
 1               5                  10                  15
Lys Val Thr Arg Ile Gln Ser Met Asn Tyr Gly Thr Ile Lys Trp Phe
            20                  25                  30
Phe His Val Ile Ile Phe Ser Tyr Val Cys Phe Ala Leu Val Ser Asp
        35                  40                  45
Lys Leu Tyr Gln Arg Lys Glu Pro Val Ile Ser Ser Val His Thr Lys
    50                  55                  60
Val Lys Gly Ile Ala Glu Val Lys Glu Glu Ile Val Glu Asn Gly Val
65                  70                  75                  80
Lys Lys Leu Val His Ser Val Phe Asp Thr Ala Asp Tyr Thr Phe Pro
                85                  90                  95
Leu Gln Gly Asn Ser Phe Phe Val Met Thr Asn Phe Leu Lys Thr Glu
            100                 105                 110
Gly Gln Glu Gln Arg Leu Cys Pro Glu Tyr Pro Thr Arg Arg Thr Leu
        115                 120                 125
Cys Ser Ser Asp Arg Gly Cys Lys Lys Gly Trp Met Asp Pro Gln Ser
    130                 135                 140
Lys Gly Ile Gln Thr Gly Arg Cys Val Val His Glu Gly Asn Gln Lys
145                 150                 155                 160
Thr Cys Glu Val Ser Ala Trp Cys Pro Ile Glu Ala Val Glu Glu Ala
                165                 170                 175
Pro Arg Pro Ala Leu Leu Asn Ser Ala Glu Asn Phe Thr Val Leu Ile
            180                 185                 190
Lys Asn Asn Ile Asp Phe Pro Gly His Asn Tyr Thr Thr Arg Asn Ile
        195                 200                 205
Leu Pro Gly Leu Asn Ile Thr Cys Thr Phe His Lys Thr Gln Asn Pro
    210                 215                 220
Gln Cys Pro Ile Phe Arg Leu Gly Asp Ile Phe Arg Glu Thr Gly Asp
225                 230                 235                 240
Asn Phe Ser Asp Val Ala Ile Gln Gly Gly Ile Met Gly Ile Glu Ile
                245                 250                 255
Tyr Trp Asp Cys Asn Leu Asp Arg Trp Phe His His Cys His Pro Lys
            260                 265                 270
Tyr Ser Phe Arg Arg Leu Asp Asp Lys Thr Thr Asn Val Ser Leu Tyr
        275                 280                 285
Pro Gly Tyr Asn Phe Arg Tyr Ala Lys Tyr Tyr Lys Glu Asn Asn Val
    290                 295                 300
Glu Lys Arg Thr Leu Ile Lys Val Phe Gly Ile Arg Phe Asp Ile Leu
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305                 310                 315                 320
Val Phe Gly Thr Gly Gly Lys Phe Asp Ile Ile Gln Leu Val Val Tyr
                325                 330                 335
Ile Gly Ser Thr Leu Ser Tyr Phe Gly Leu Ala Ala Val Phe Ile Asp
            340                 345                 350
Phe Leu Ile Asp Thr Tyr Ser Ser Asn Cys Cys Arg Ser His Ile Tyr
        355                 360                 365
Pro Trp Cys Lys Cys Cys Gln Pro Cys Val Val Asn Glu Tyr Tyr Tyr
    370                 375                 380
Arg Lys Lys Cys Glu Ser Ile Val Glu Pro Lys Pro Thr Leu Lys Tyr
385                 390                 395                 400
Val Ser Phe Val Asp Glu Ser His Ile Arg Met Val Asn Gln Gln Leu
                405                 410                 415
Leu Gly Arg Ser Leu Gln Asp Val Lys Gly Gln Glu Val Pro Arg Pro
            420                 425                 430
Ala Met Asp Phe Thr Asp Leu Ser Arg Leu Pro Leu Ala Leu His Asp
        435                 440                 445
Thr Pro Pro Ile Pro Gly Gln Pro Glu Glu Ile Gln Leu Leu Arg Lys
    450                 455                 460
Glu Ala Thr Pro Arg Ser Arg Asp Ser Pro Val Trp Cys Gln Cys Gly
465                 470                 475                 480
Ser Cys Leu Pro Ser Gln Leu Pro Glu Ser His Arg Cys Leu Glu Glu
                485                 490                 495
Leu Cys Cys Arg Lys Lys Pro Gly Ala Cys Ile Thr Thr Ser Glu Leu
            500                 505                 510
Phe Arg Lys Leu Val Leu Ser Arg His Val Leu Gln Phe Leu Leu Leu
        515                 520                 525
Tyr Gln Glu Pro Leu Leu Ala Leu Asp Val Asp Ser Thr Asn Ser Arg
    530                 535                 540
Leu Arg His Cys Ala Tyr Arg Cys Tyr Ala Thr Trp Arg Phe Gly Ser
545                 550                 555                 560
Gln Asp Met Ala Asp Phe Ala Ile Leu Pro Ser Cys Cys Arg Trp Arg
                565                 570                 575
Ile Arg Lys Glu Phe Pro Lys Ser Glu Gly Gln Tyr Ser Gly Phe Lys
            580                 585                 590
Ser Pro Tyr
        595
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<210> 41
<211> 1700
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (125)...(1585)

<400> 41
cggaattggt gggttcttgg tctcactgag ttctagaatg aagctgcaga ccctcgcagt 60
gagtgttaca gctcttaagg ctctctgact gccacccctg cctgcctgcc cggccctgca 120
caac atg cag ccc tcc ggc ctc gag ggt ccc ggc acg ttt ggt cgg tgg 169
     Met Gln Pro Ser Gly Leu Glu Gly Pro Gly Thr Phe Gly Arg Trp
      1   5   10   15

cct ctg ctg agt ctg ctg ctc ctg ctg ctg ctg ctc cag cct gta acc 217
Pro Leu Leu Ser Leu Leu Leu Leu Leu Leu Leu Gln Pro Val Thr
                  20   25   30

tgt gcc tac acc acg cca ggc ccc ccc aga gcc ctc acc acg ctg ggc 265

```
Cys Ala Tyr Thr Thr Pro Gly Pro Pro Arg Ala Leu Thr Thr Leu Gly
                35                  40                  45

gcc ccc aga gcc cac acc atg ccg ggc acc tac gct ccc tcg acc aca   313
Ala Pro Arg Ala His Thr Met Pro Gly Thr Tyr Ala Pro Ser Thr Thr
         50                  55                  60

ctc agt agt ccc agc acc cag ggc ctg caa gag cag gca cgg gcc ctg   361
Leu Ser Ser Pro Ser Thr Gln Gly Leu Gln Glu Gln Ala Arg Ala Leu
     65                  70                  75

atg cgg gac ttc ccg ctc gtg gac ggc cac aac gac ctg ccc ctg gtc   409
Met Arg Asp Phe Pro Leu Val Asp Gly His Asn Asp Leu Pro Leu Val
 80                  85                  90                  95

cta agg cag gtt tac cag aaa ggg cta cag gat gtt aac ctg cgc aat   457
Leu Arg Gln Val Tyr Gln Lys Gly Leu Gln Asp Val Asn Leu Arg Asn
                100                 105                 110

ttc agc tac ggc cag acc agc ctg gac agg ctt aga gat ggc ctc gtg   505
Phe Ser Tyr Gly Gln Thr Ser Leu Asp Arg Leu Arg Asp Gly Leu Val
            115                 120                 125

ggc gcc cag ttc tgg tca gcc tat gtg cca tgc cag acc cag gac cgg   553
Gly Ala Gln Phe Trp Ser Ala Tyr Val Pro Cys Gln Thr Gln Asp Arg
        130                 135                 140

gat gcc ctg cgc ctc acc ctg gag cag att gac ctc ata cgc cgc atg   601
Asp Ala Leu Arg Leu Thr Leu Glu Gln Ile Asp Leu Ile Arg Arg Met
    145                 150                 155

tgt gcc tcc tat tct gag ctg gag ctt gtg acc tcg gct aaa gct ctg   649
Cys Ala Ser Tyr Ser Glu Leu Glu Leu Val Thr Ser Ala Lys Ala Leu
160                 165                 170                 175

aac gac act cag aaa ttg gcc tgc ctc atc ggt gta gag ggt ggc cac   697
Asn Asp Thr Gln Lys Leu Ala Cys Leu Ile Gly Val Glu Gly Gly His
                180                 185                 190

tcg ctg gac aat agc ctc tcc atc tta cgt acc ttc tac atg ctg gga   745
Ser Leu Asp Asn Ser Leu Ser Ile Leu Arg Thr Phe Tyr Met Leu Gly
            195                 200                 205

gtg cgc tac ctg acg ctc acc cac acc tgc aac aca ccc tgg gca gag   793
Val Arg Tyr Leu Thr Leu Thr His Thr Cys Asn Thr Pro Trp Ala Glu
        210                 215                 220

agc tcc gct aag ggc gtc cac tcc ttc tac aac aac atc agc ggg ctg   841
Ser Ser Ala Lys Gly Val His Ser Phe Tyr Asn Asn Ile Ser Gly Leu
    225                 230                 235

act gac ttt ggt gag aag gtg gtg gca gaa atg aac cgc ctg ggc atg   889
Thr Asp Phe Gly Glu Lys Val Val Ala Glu Met Asn Arg Leu Gly Met
240                 245                 250                 255

atg gta gac tta tcc cat gtc tca gat gct gtg gca cgg cgg gcc ctg   937
Met Val Asp Leu Ser His Val Ser Asp Ala Val Ala Arg Arg Ala Leu
                260                 265                 270

gaa gtg tca cag gca cct gtg atc ttc tcc cac tcg gct gcc cgg ggt   985
Glu Val Ser Gln Ala Pro Val Ile Phe Ser His Ser Ala Ala Arg Gly
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            275                 280                 285

gtg tgc aac agt gct cgg aat gtt cct gat gac atc ctg cag ctt ctg   1033
Val Cys Asn Ser Ala Arg Asn Val Pro Asp Asp Ile Leu Gln Leu Leu
        290                 295                 300

aag aag aac ggt ggc gtc gtg atg gtg tct ttg tcc atg gga gta ata   1081
Lys Lys Asn Gly Gly Val Val Met Val Ser Leu Ser Met Gly Val Ile
    305                 310                 315

cag tgc aac cca tca gcc aat gtg tcc act gtg gca gat cac ttc gac   1129
Gln Cys Asn Pro Ser Ala Asn Val Ser Thr Val Ala Asp His Phe Asp
320                 325                 330                 335

cac atc aag gct gtc att gga tcc aag ttc atc ggg att ggt gga gat   1177
His Ile Lys Ala Val Ile Gly Ser Lys Phe Ile Gly Ile Gly Gly Asp
                340                 345                 350

tat gat ggg gcc ggc aaa ttc cct cag ggg ctg gaa gac gtg tcc aca   1225
Tyr Asp Gly Ala Gly Lys Phe Pro Gln Gly Leu Glu Asp Val Ser Thr
            355                 360                 365

tac ccg gtc ctg ata gag gag ttg ctg agt cgt ggc tgg agt gag gaa   1273
Tyr Pro Val Leu Ile Glu Glu Leu Leu Ser Arg Gly Trp Ser Glu Glu
        370                 375                 380

gag ctt cag ggt gtc ctt cgt gga aac ctg ctg cgg gtc ttc aga caa   1321
Glu Leu Gln Gly Val Leu Arg Gly Asn Leu Leu Arg Val Phe Arg Gln
    385                 390                 395

gtg gaa aag gta cag gaa gaa aac aaa tgg caa agc ccc ttg gag gac   1369
Val Glu Lys Val Gln Glu Glu Asn Lys Trp Gln Ser Pro Leu Glu Asp
400                 405                 410                 415

aag ttc ccg gat gag cag ctg agc agt tcc tgc cac tcc gac ctc tca   1417
Lys Phe Pro Asp Glu Gln Leu Ser Ser Ser Cys His Ser Asp Leu Ser
                420                 425                 430

cgt ctg cgt cag aga cag agt ctg act tca ggc cag gaa ctc act gag   1465
Arg Leu Arg Gln Arg Gln Ser Leu Thr Ser Gly Gln Glu Leu Thr Glu
            435                 440                 445

att ccc ata cac tgg aca gcc aag tta cca gcc aag tgg tca gtc tca   1513
Ile Pro Ile His Trp Thr Ala Lys Leu Pro Ala Lys Trp Ser Val Ser
        450                 455                 460

gag tcc tcc ccc cac atg gcc cca gtc ctt gca gtt gtg gcc acc ttc   1561
Glu Ser Ser Pro His Met Ala Pro Val Leu Ala Val Val Ala Thr Phe
    465                 470                 475

cca gtc ctt att ctg tgg ctc tga tgacccagtt agtcctgcca gatgtcactg  1615
Pro Val Leu Ile Leu Trp Leu  *
480                 485

tagcaagcca cagacacccc acaaagttcc cctgttgtgc aggcacaaat atttcttgaa 1675
ataaatgttt tggacataga aaaaa                                      1700

<210> 42
<211> 486
<212> PRT
<213> Homo sapiens
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<400> 42

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Met Gln Pro Ser Gly Leu Glu Gly Pro Gly Thr Phe Gly Arg Trp Pro
 1               5                  10                  15
Leu Leu Ser Leu Leu Leu Leu Leu Leu Leu Leu Gln Pro Val Thr Cys
            20                  25                  30
Ala Tyr Thr Thr Pro Gly Pro Pro Arg Ala Leu Thr Thr Leu Gly Ala
        35                  40                  45
Pro Arg Ala His Thr Met Pro Gly Thr Tyr Ala Pro Ser Thr Thr Leu
    50                  55                  60
Ser Ser Pro Ser Thr Gln Gly Leu Gln Glu Gln Ala Arg Ala Leu Met
65                  70                  75                  80
Arg Asp Phe Pro Leu Val Asp Gly His Asn Asp Leu Pro Leu Val Leu
                85                  90                  95
Arg Gln Val Tyr Gln Lys Gly Leu Gln Asp Val Asn Leu Arg Asn Phe
            100                 105                 110
Ser Tyr Gly Gln Thr Ser Leu Asp Arg Leu Arg Asp Gly Leu Val Gly
        115                 120                 125
Ala Gln Phe Trp Ser Ala Tyr Val Pro Cys Gln Thr Gln Asp Arg Asp
    130                 135                 140
Ala Leu Arg Leu Thr Leu Glu Gln Ile Asp Leu Ile Arg Arg Met Cys
145                 150                 155                 160
Ala Ser Tyr Ser Glu Leu Glu Leu Val Thr Ser Ala Lys Ala Leu Asn
                165                 170                 175
Asp Thr Gln Lys Leu Ala Cys Leu Ile Gly Val Glu Gly Gly His Ser
            180                 185                 190
Leu Asp Asn Ser Leu Ser Ile Leu Arg Thr Phe Tyr Met Leu Gly Val
        195                 200                 205
Arg Tyr Leu Thr Leu Thr His Thr Cys Asn Thr Pro Trp Ala Glu Ser
    210                 215                 220
Ser Ala Lys Gly Val His Ser Phe Tyr Asn Asn Ile Ser Gly Leu Thr
225                 230                 235                 240
Asp Phe Gly Glu Lys Val Val Ala Glu Met Asn Arg Leu Gly Met Met
                245                 250                 255
Val Asp Leu Ser His Val Ser Asp Ala Val Ala Arg Arg Ala Leu Glu
            260                 265                 270
Val Ser Gln Ala Pro Val Ile Phe Ser His Ser Ala Ala Arg Gly Val
        275                 280                 285
Cys Asn Ser Ala Arg Asn Val Pro Asp Asp Ile Leu Gln Leu Leu Lys
    290                 295                 300
Lys Asn Gly Gly Val Val Met Val Ser Leu Ser Met Gly Val Ile Gln
305                 310                 315                 320
Cys Asn Pro Ser Ala Asn Val Ser Thr Val Ala Asp His Phe Asp His
                325                 330                 335
Ile Lys Ala Val Ile Gly Ser Lys Phe Ile Gly Ile Gly Gly Asp Tyr
            340                 345                 350
Asp Gly Ala Gly Lys Phe Pro Gln Gly Leu Glu Asp Val Ser Thr Tyr
        355                 360                 365
Pro Val Leu Ile Glu Glu Leu Leu Ser Arg Gly Trp Ser Glu Glu Glu
    370                 375                 380
Leu Gln Gly Val Leu Arg Gly Asn Leu Leu Arg Val Phe Arg Gln Val
385                 390                 395                 400
Glu Lys Val Gln Glu Glu Asn Lys Trp Gln Ser Pro Leu Glu Asp Lys
                405                 410                 415
Phe Pro Asp Glu Gln Leu Ser Ser Ser Cys His Ser Asp Leu Ser Arg
            420                 425                 430
Leu Arg Gln Arg Gln Ser Leu Thr Ser Gly Gln Glu Leu Thr Glu Ile
        435                 440                 445
Pro Ile His Trp Thr Ala Lys Leu Pro Ala Lys Trp Ser Val Ser Glu
    450                 455                 460
Ser Ser Pro His Met Ala Pro Val Leu Ala Val Val Ala Thr Phe Pro
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465                 470                 475                 480
Val Leu Ile Leu Trp Leu
                485

<210> 43
<211> 2850
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (81)...(1826)

<400> 43
ccggctcggt accactataa cggccgccag tgtgctggaa ttcgcccttg cgcagatcgc 60
tggctgcagt tggcgggcgc atg tgg ggg cgc acg gcg cgg cgg cgc tgc ccg 113
                       Met Trp Gly Arg Thr Ala Arg Arg Arg Cys Pro
                        1               5                  10

cgg gaa ctg cgg cgc ggc cgg gag gcg ctg ttg gtg ctc ctg gcg cta   161
Arg Glu Leu Arg Arg Gly Arg Glu Ala Leu Leu Val Leu Leu Ala Leu
            15                  20                  25

ctg gcg ttg gcc ggg ctg ggc tcg gtg ctg cgg gcg cag cgt ggg gcc   209
Leu Ala Leu Ala Gly Leu Gly Ser Val Leu Arg Ala Gln Arg Gly Ala
        30                  35                  40

ggg gcc ggg gct gcc gag ccg gga ccc ccg cgc acc ccg cgc ccc ggg   257
Gly Ala Gly Ala Ala Glu Pro Gly Pro Pro Arg Thr Pro Arg Pro Gly
    45                  50                  55

cgg cgc gag ccg gtc atg ccg cgg ccg ccg gtg ccg gcg aac gcg ctg   305
Arg Arg Glu Pro Val Met Pro Arg Pro Pro Val Pro Ala Asn Ala Leu
60                  65                  70                  75

ggc gcg cgg ggc gag gcg gtg cgg ctg cag ctg cag ggc gag gag ctg   353
Gly Ala Arg Gly Glu Ala Val Arg Leu Gln Leu Gln Gly Glu Glu Leu
                80                  85                  90

cgg ctg cag gag gag agc gtg cgg ctg cac cag att aac atc tac ctc   401
Arg Leu Gln Glu Glu Ser Val Arg Leu His Gln Ile Asn Ile Tyr Leu
            95                  100                 105

agc gac cgc atc tca ctg cac cgc cgc ctg ccc gag cgc tgg aac ccg   449
Ser Asp Arg Ile Ser Leu His Arg Arg Leu Pro Glu Arg Trp Asn Pro
        110                 115                 120

ctg tgc aaa gag aag aaa tat gat tat gat aat ttg ccc agg aca tct   497
Leu Cys Lys Glu Lys Lys Tyr Asp Tyr Asp Asn Leu Pro Arg Thr Ser
    125                 130                 135

gtt atc ata gca ttt tat aat gaa gcc tgg tca act ctc ctt cgg aca   545
Val Ile Ile Ala Phe Tyr Asn Glu Ala Trp Ser Thr Leu Leu Arg Thr
140                 145                 150                 155

gtt tac agt gtc ctt gag aca tcc ccg gat atc ctg cta gaa gaa gtg   593
Val Tyr Ser Val Leu Glu Thr Ser Pro Asp Ile Leu Leu Glu Glu Val
                160                 165                 170
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atc ctt gta gat gac tac agt gat aga gag cac ctg aag gag cgc ttg   641
Ile Leu Val Asp Asp Tyr Ser Asp Arg Glu His Leu Lys Glu Arg Leu
            175                 180                 185

gcc aat gag ctt tcg gga ctg ccc aag gtg cgc ctg atc cgc gcc aac   689
Ala Asn Glu Leu Ser Gly Leu Pro Lys Val Arg Leu Ile Arg Ala Asn
        190                 195                 200

aag aga gag ggc ctg gtg cga gcc cgg ctg ctg ggg gcg tct gcg gcg   737
Lys Arg Glu Gly Leu Val Arg Ala Arg Leu Leu Gly Ala Ser Ala Ala
    205                 210                 215

agg ggc gat gtt ctg acc ttc ctg gac tgt cac tgt gag tgc cac gaa   785
Arg Gly Asp Val Leu Thr Phe Leu Asp Cys His Cys Glu Cys His Glu
220                 225                 230                 235

ggg tgg ctg gag ccg ctg ctg cag agg atc cat gaa gag gag tcg gca   833
Gly Trp Leu Glu Pro Leu Leu Gln Arg Ile His Glu Glu Glu Ser Ala
                240                 245                 250

gtg gtg tgc ccg gtg att gat gtg atc gac tgg aac acc ttc gaa tac   881
Val Val Cys Pro Val Ile Asp Val Ile Asp Trp Asn Thr Phe Glu Tyr
            255                 260                 265

ctg ggg aac tcc ggg gag ccc cag atc ggc ggt ttc gac tgg agg ctg   929
Leu Gly Asn Ser Gly Glu Pro Gln Ile Gly Gly Phe Asp Trp Arg Leu
        270                 275                 280

gtg ttc acg tgg cac aca gtt cct gag agg gag agg ata cgg atg caa   977
Val Phe Thr Trp His Thr Val Pro Glu Arg Glu Arg Ile Arg Met Gln
    285                 290                 295

tcc ccc gtc gat gtc atc agg tct cca aca atg gct ggt ggg ctg ttt   1025
Ser Pro Val Asp Val Ile Arg Ser Pro Thr Met Ala Gly Gly Leu Phe
300                 305                 310                 315

gct gtg agt aag aaa tat ttt gaa tat ctg ggg tct tat gat aca gga   1073
Ala Val Ser Lys Lys Tyr Phe Glu Tyr Leu Gly Ser Tyr Asp Thr Gly
                320                 325                 330

atg gaa gtt tgg gga gga gaa aac ctc gaa ttt tcc ttt agg atc tgg   1121
Met Glu Val Trp Gly Gly Glu Asn Leu Glu Phe Ser Phe Arg Ile Trp
            335                 340                 345

cag tgt ggt ggg gtt ctg gaa aca cac cca tgt tcc cat gtt ggc cat   1169
Gln Cys Gly Gly Val Leu Glu Thr His Pro Cys Ser His Val Gly His
        350                 355                 360

gtt ttc ccc aag caa gct ccc tac tcc cgc aac aag gct ctg gcc aac   1217
Val Phe Pro Lys Gln Ala Pro Tyr Ser Arg Asn Lys Ala Leu Ala Asn
    365                 370                 375

agt gtt cgt gca gct gaa gta tgg atg gat gaa ttt aaa gag ctc tac   1265
Ser Val Arg Ala Ala Glu Val Trp Met Asp Glu Phe Lys Glu Leu Tyr
380                 385                 390                 395

tac cat cgc aac ccc cgt gcc cgc ttg gaa cct ttt ggg gat gtg aca   1313
Tyr His Arg Asn Pro Arg Ala Arg Leu Glu Pro Phe Gly Asp Val Thr
                400                 405                 410

gag agg aag cag ctc cgg gac aag ctc cag tgt aaa gac ttc aag tgg   1361
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```
Glu Arg Lys Gln Leu Arg Asp Lys Leu Gln Cys Lys Asp Phe Lys Trp
            415                 420                 425

ttc ttg gag act gtg tat cca gaa ctg cat gtg cct gag gac agg cct   1409
Phe Leu Glu Thr Val Tyr Pro Glu Leu His Val Pro Glu Asp Arg Pro
        430                 435                 440

ggc ttc ttc ggg atg ctc cag aac aaa gga cta aca gac tac tgc ttt   1457
Gly Phe Phe Gly Met Leu Gln Asn Lys Gly Leu Thr Asp Tyr Cys Phe
    445                 450                 455

gac tat aac cct ccc gat gaa aac cag att gtg gga cac cag gtc att   1505
Asp Tyr Asn Pro Pro Asp Glu Asn Gln Ile Val Gly His Gln Val Ile
460                 465                 470                 475

ctg tac ctc tgt cat ggg atg ggc cag aat cag ttt ttc gag tac acg   1553
Leu Tyr Leu Cys His Gly Met Gly Gln Asn Gln Phe Phe Glu Tyr Thr
                480                 485                 490

tcc cag aaa gaa ata cgc tat aac acc cac cag cct gag ggc tgc att   1601
Ser Gln Lys Glu Ile Arg Tyr Asn Thr His Gln Pro Glu Gly Cys Ile
            495                 500                 505

gct gtg gaa gca gga atg gat acc ctt atc atg cat ctc tgc gaa gaa   1649
Ala Val Glu Ala Gly Met Asp Thr Leu Ile Met His Leu Cys Glu Glu
        510                 515                 520

act gcc cca gag aat cag aag ttc atc ttg cag gag gat gga tct tta   1697
Thr Ala Pro Glu Asn Gln Lys Phe Ile Leu Gln Glu Asp Gly Ser Leu
    525                 530                 535

ttt cac gaa cag tcc aag aaa tgt gtc cag gct gcg agg aag gag tcg   1745
Phe His Glu Gln Ser Lys Lys Cys Val Gln Ala Ala Arg Lys Glu Ser
540                 545                 550                 555

agt gac agt ttc gtt cca ctc tta cga gac tgc acc aac tcg gat cat   1793
Ser Asp Ser Phe Val Pro Leu Leu Arg Asp Cys Thr Asn Ser Asp His
                560                 565                 570

cag aaa tgg ttc ttc aaa gag cgc atg tta tga agcctcgtgt atcaaggagc 1846
Gln Lys Trp Phe Phe Lys Glu Arg Met Leu  *
            575                 580

ccatcgaagg agactgtgga gccaggactc tgcccaacaa agacttagct aagcagtgac 1906
cagaacccac caaaaactag gctgcattgc tttgaagagg caatcatttt gccatttgtg 1966
aaagttgtgt tggatttagt aaaaatgtga ataagctttg tacttatttt gagaactttt 2026
taaatgttcc aaaataccct attttcaaag ggtaatcgta agatgttaac ccttggtatt 2086
tagaaaatta aaaccttata atatttttct atcaarawrw awattttaca gtcgtgcctt 2146
ttactctcat tagcaaaaaa gataaagatt ttattttggt atttacaaga attcccaggt 2206
acgaagatat ctgcatgggt ggaaatcagg ttcaagcaac gtactttgca ttaactgata 2266
atacctcagc tgcggggtta aagttttccc agtatagaga gactgtcact aggaacattg 2326
tattgattta ttcaggtcat tgagatcttc tagatgtatt ttaaaaagaa tgctttttgg 2386
ttatgtgttg ctaccacagt taacactcca taatgttcat gtcagccaaa gaggactaac 2446
caaagctgaa atctcagaga acaatttgct ttactaagct gagtcaactt gagagcgaac 2506
ttctaacaat gccgcactgt agtgtggctg gttctaccac tatgacttta aaacatgttt 2566
atatcatttt taatttttat gatacggtag tgtcagggag aaatgtaatg ttctatatga 2626
aattcctttt tcaagtttgt tcattaataa cagttattaa tttaaatcag cgttagagtt 2686
tgtgctgctg caactgctgt gaaaatttct ctgagtaatt ctgatttgtg aatgatccca 2746
gaccaaccct gagattttgt caacctgatt aagtcaatat gaatgattaa aaagatgtga 2806
gaacaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa                  2850
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<210> 44
<211> 581
<212> PRT
<213> Homo sapiens

<400> 44
Met Trp Gly Arg Thr Ala Arg Arg Arg Cys Pro Arg Glu Leu Arg Arg
1 5 10 15
Gly Arg Glu Ala Leu Leu Val Leu Leu Ala Leu Leu Ala Leu Ala Gly
20 25 30
Leu Gly Ser Val Leu Arg Ala Gln Arg Gly Ala Gly Ala Gly Ala Ala
35 40 45
Glu Pro Gly Pro Pro Arg Thr Pro Arg Pro Gly Arg Arg Glu Pro Val
50 55 60
Met Pro Arg Pro Pro Val Pro Ala Asn Ala Leu Gly Ala Arg Gly Glu
65 70 75 80
Ala Val Arg Leu Gln Leu Gln Gly Glu Glu Leu Arg Leu Gln Glu Glu
85 90 95
Ser Val Arg Leu His Gln Ile Asn Ile Tyr Leu Ser Asp Arg Ile Ser
100 105 110
Leu His Arg Arg Leu Pro Glu Arg Trp Asn Pro Leu Cys Lys Glu Lys
115 120 125
Lys Tyr Asp Tyr Asp Asn Leu Pro Arg Thr Ser Val Ile Ile Ala Phe
130 135 140
Tyr Asn Glu Ala Trp Ser Thr Leu Leu Arg Thr Val Tyr Ser Val Leu
145 150 155 160
Glu Thr Ser Pro Asp Ile Leu Leu Glu Glu Val Ile Leu Val Asp Asp
165 170 175
Tyr Ser Asp Arg Glu His Leu Lys Glu Arg Leu Ala Asn Glu Leu Ser
180 185 190
Gly Leu Pro Lys Val Arg Leu Ile Arg Ala Asn Lys Arg Glu Gly Leu
195 200 205
Val Arg Ala Arg Leu Leu Gly Ala Ser Ala Ala Arg Gly Asp Val Leu
210 215 220
Thr Phe Leu Asp Cys His Cys Glu Cys His Glu Gly Trp Leu Glu Pro
225 230 235 240
Leu Leu Gln Arg Ile His Glu Glu Glu Ser Ala Val Val Cys Pro Val
245 250 255
Ile Asp Val Ile Asp Trp Asn Thr Phe Glu Tyr Leu Gly Asn Ser Gly
260 265 270
Glu Pro Gln Ile Gly Gly Phe Asp Trp Arg Leu Val Phe Thr Trp His
275 280 285
Thr Val Pro Glu Arg Glu Arg Ile Arg Met Gln Ser Pro Val Asp Val
290 295 300
Ile Arg Ser Pro Thr Met Ala Gly Gly Leu Phe Ala Val Ser Lys Lys
305 310 315 320
Tyr Phe Glu Tyr Leu Gly Ser Tyr Asp Thr Gly Met Glu Val Trp Gly
325 330 335
Gly Glu Asn Leu Glu Phe Ser Phe Arg Ile Trp Gln Cys Gly Gly Val
340 345 350
Leu Glu Thr His Pro Cys Ser His Val Gly His Val Phe Pro Lys Gln
355 360 365
Ala Pro Tyr Ser Arg Asn Lys Ala Leu Ala Asn Ser Val Arg Ala Ala
370 375 380
Glu Val Trp Met Asp Glu Phe Lys Glu Leu Tyr Tyr His Arg Asn Pro
385 390 395 400
Arg Ala Arg Leu Glu Pro Phe Gly Asp Val Thr Glu Arg Lys Gln Leu
405 410 415
Arg Asp Lys Leu Gln Cys Lys Asp Phe Lys Trp Phe Leu Glu Thr Val
420 425 430
Tyr Pro Glu Leu His Val Pro Glu Asp Arg Pro Gly Phe Phe Gly Met

```
        435                 440                 445
Leu Gln Asn Lys Gly Leu Thr Asp Tyr Cys Phe Asp Tyr Asn Pro Pro
    450                 455                 460
Asp Glu Asn Gln Ile Val Gly His Gln Val Ile Leu Tyr Leu Cys His
465                 470                 475                 480
Gly Met Gly Gln Asn Gln Phe Phe Glu Tyr Thr Ser Gln Lys Glu Ile
                485                 490                 495
Arg Tyr Asn Thr His Gln Pro Glu Gly Cys Ile Ala Val Glu Ala Gly
            500                 505                 510
Met Asp Thr Leu Ile Met His Leu Cys Glu Glu Thr Ala Pro Glu Asn
        515                 520                 525
Gln Lys Phe Ile Leu Gln Glu Asp Gly Ser Leu Phe His Glu Gln Ser
    530                 535                 540
Lys Lys Cys Val Gln Ala Ala Arg Lys Glu Ser Ser Asp Ser Phe Val
545                 550                 555                 560
Pro Leu Leu Arg Asp Cys Thr Asn Ser Asp His Gln Lys Trp Phe Phe
                565                 570                 575
Lys Glu Arg Met Leu
            580
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<210> 45
<211> 2890
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (229)...(1116)

<400> 45

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gtcgcagatt caaacaaata gcagcgaaca gggaatgaca gttccaccag aagacgatta 60
agccacagcc tctaattgga acggcatttg tacagtcaga gactcttacc agacatctcc 120
aggaatctgt gagccattgt caaaacgtcc attttcatct ggctgtgaaa gtgaggacca 180
caacaggtag gtattggtag aaacaggagt cctcagagaa gccccaag atg cag cct  237
                                                    Met Gln Pro
                                                     1

gag gga gca gaa aag gga aaa agc ttc aag cag aga ctg gtc ttg aag   285
Glu Gly Ala Glu Lys Gly Lys Ser Phe Lys Gln Arg Leu Val Leu Lys
     5                  10                  15

agc agc tta gcg aaa gaa acc ctc tct gag ttc ttg ggc acg ttc atc   333
Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly Thr Phe Ile
 20                  25                  30                  35

ttg att gtc ctt gga tgt ggc tgt gtt gcc caa gct att ctc agt cga   381
Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile Leu Ser Arg
                 40                  45                  50

gga cgt ttt gga ggg gtc atc act atc aat gtt gga ttt tca atg gca   429
Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe Ser Met Ala
            55                  60                  65

gtt gca atg gcc att tat gtg gct ggc ggt gtc tct ggt ggt cac atc   477
Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly Gly His Ile
         70                  75                  80

aac cca gct gtg tct tta gca atg tgt ctc ttt gga cgg atg aaa tgg   525
Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg Met Lys Trp
     85                  90                  95
```

```
ttc aaa ttg cca ttt tat gtg gga gcc cag ttc ttg gga gcc ttt gtg   573
Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly Ala Phe Val
100                 105                 110                 115

ggg gct gca acc gtc ttt ggc att tac tat gat gga ctt atg tcc ttt   621
Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu Met Ser Phe
                120                 125                 130

gct ggt gga aaa ctg ctg atc gtg gga gaa aat gca aca gca cac att   669
Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr Ala His Ile
            135                 140                 145

ttt gca aca tac cca gct ccg tat cta tct ctg gcg aac gca ttt gca   717
Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn Ala Phe Ala
        150                 155                 160

gat caa gtg gtg gcc acc atg ata ctc ctc ata atc gtc ttt gcc att   765
Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val Phe Ala Ile
    165                 170                 175

ttt gac tcc aga aac ttg gga gcc ccc aga ggc cta gag ccc att gcc   813
Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu Pro Ile Ala
180                 185                 190                 195

atc ggc ctc ctg att att gtc att gct tcc tcc ctg gga ctg aac agt   861
Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly Leu Asn Ser
                200                 205                 210

ggc tgt gcc atg aac cca gct cga gac ctg agt ccc aga ctt ttc act   909
Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg Leu Phe Thr
            215                 220                 225

gcc ttg gca ggc tgg ggg ttt gaa gtc ttc aga gct gga aac aac ttc   957
Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly Asn Asn Phe
        230                 235                 240

tgg tgg att cct gta gtg ggc cct ttg gtt ggt gct gtc att gga ggc   1005
Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val Ile Gly Gly
    245                 250                 255

ctc atc tat gtt ctt gtc att gaa atc cac cat cca gag cct gac tca   1053
Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu Pro Asp Ser
260                 265                 270                 275

gtc ttt aag gca gaa caa tct gag gac aaa cca gag aaa tat gaa ctc   1101
Val Phe Lys Ala Glu Gln Ser Glu Asp Lys Pro Glu Lys Tyr Glu Leu
                280                 285                 290

agt gtc atc atg tag tggcatgctc agctctggat ttgcagtcag tttgggattc   1156
Ser Val Ile Met  *
            295

tcttcagaaa gatggcatct aagtgtctgt gttcttgtaa gcctgaggtg gaatccaccc 1216
agttttgtct gctagccata tgggacatct aattggaaaa gcatctgcat aaaagtttgg 1276
aaacaatgac cacttctcta ccattgtccc ccaccccacc ccccagaata acgctgactg 1336
tcccctgaaa cagccttctc tcctgccctg tttatttcat cctcgatggg aattcttgct 1396
aggtaagcac taataactcg gcatcttgac gatagtccca tttgggtggt ttcagctgca 1456
ctatctgtat gaaatggtgt caccaaaacc cttttcttca gtatcgacaa agattacatt 1516
ctgagtacca accaaaccct aaattgaaag acaaaactat ggtttcagtc aacatattca 1576
tgaattaggg agctaatggg ttaagcttcc agttcccgct atgctactgg atttgtataa 1636
```

```
atactgatat tctccaaacc tagtggtgta gggagcaaga gaatgcagct ggaaggcaca 1696
aggggaggac attgtggcat tcagaaactg caggagacaa gatgaatttg agaagccaaa 1756
tggaattttt aatggaaacc atttatcaga ttaatctctt gctctcctgc attttagagg 1816
acaccaatta atttcctggt ctttagtata taataaccta aaataccatt gtaacctcag 1876
tcatgaaaaa tacatcactc tgtcttttta gctcaaatgt attttcctaa ttgcccactt 1936
gagaacagac atttgacaag ttatatcaac gactgtgctt gtccattatt ttacacatgc 1996
cctagaagcc aaaactgaaa gccactggat cctggtctag ctgaatcttc agagtgggag 2056
gtctccaaaa agatattacc ttattgggct taacaattca caaggcactt tcacacccat 2116
tatctaattt aatcctcata atgactatgt gaggcaaatg ccacattgcc cattttcag 2176
ataaagaaac aaaatcttag ggaagataag ttgagttgtc caagagcaca ctgaaagttg 2236
aatgttatct aatgcattcc tctacctttc agaagatcag tagctggctg agaatctttg 2296
ccaaatcttc cttgctagcc agaagtggaa ttggcagctt ctagaatatg tacacctctg 2356
gacaaaatgt tcctcaatct taagatacaa agaccctcat tgtctgggtc tattcccaca 2416
cttactgagt acagatgaag gaaagtggta gcaatttaat cataactttc atttgctgaa 2476
aaacattatg agaaggcctc ccttcctaag ccacctctgg tcttgctaag tcttgatctt 2536
gcttcctgcc agcaccaaac attacattca ggggatttcc tctggctcag tcttttcccc 2596
ttgaagttct ctaatagatg ttacttttga caaaagatcg cctatgagtt acaagcacca 2656
ggggatgctc tacatcaagg gatgcacctt cagtcaaact gtcaaaaagc ccagaattcc 2716
caaaggcatt aggtttccca actgctttgt gctgatatca gaacagcaga aattaaatgt 2776
gaaatgtttc tgatgactta tgttctacaa tctatggaca tacgggattt ttttttcttg 2836
ctttgaagct acctggatat ttcctatttg aaataaaatt gttcggtcat tgtt       2890

<210> 46
<211> 295
<212> PRT
<213> Homo sapiens

<400> 46
Met Gln Pro Glu Gly Ala Glu Lys Gly Lys Ser Phe Lys Gln Arg Leu
 1               5                  10                  15
Val Leu Lys Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly
            20                  25                  30
Thr Phe Ile Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile
        35                  40                  45
Leu Ser Arg Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe
    50                  55                  60
Ser Met Ala Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly
65                  70                  75                  80
Gly His Ile Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg
                85                  90                  95
Met Lys Trp Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly
            100                 105                 110
Ala Phe Val Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu
        115                 120                 125
Met Ser Phe Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr
    130                 135                 140
Ala His Ile Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn
145                 150                 155                 160
Ala Phe Ala Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val
                165                 170                 175
Phe Ala Ile Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu
            180                 185                 190
Pro Ile Ala Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly
        195                 200                 205
Leu Asn Ser Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg
    210                 215                 220
Leu Phe Thr Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly
225                 230                 235                 240
Asn Asn Phe Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val
                245                 250                 255
Ile Gly Gly Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu
```

```
            260                 265                 270
Pro Asp Ser Val Phe Lys Ala Glu Gln Ser Glu Asp Lys Pro Glu Lys
        275                 280                 285
Tyr Glu Leu Ser Val Ile Met
    290                 295
```

<210> 47
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1869)

<400> 47

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atg agg ctc ctc cgc aga cgc cac atg ccc ctg cgc ctg gcc atg gtg   48
Met Arg Leu Leu Arg Arg Arg His Met Pro Leu Arg Leu Ala Met Val
 1               5                  10                  15

ggc tgc gcc ttt gtg ctc ttc ctc ttc ctc ctg cat agg gat gtg agc   96
Gly Cys Ala Phe Val Leu Phe Leu Phe Leu Leu His Arg Asp Val Ser
            20                  25                  30

agc aga gag gag gcc aca gag aag ccg tgg ctg aag tcc ctg gtg agc   144
Ser Arg Glu Glu Ala Thr Glu Lys Pro Trp Leu Lys Ser Leu Val Ser
        35                  40                  45

cgg aag gat cac gtc ctg gac ctc atg ctg gag gcc atg aac aac ctt   192
Arg Lys Asp His Val Leu Asp Leu Met Leu Glu Ala Met Asn Asn Leu
    50                  55                  60

aga gat tca atg ccc aag ctc caa atc agg gct cca gaa gcc cag cag   240
Arg Asp Ser Met Pro Lys Leu Gln Ile Arg Ala Pro Glu Ala Gln Gln
65                  70                  75                  80

act ctg ttc tcc ata aac cag tcc tgc ctc cct ggg ttc tat acc cca   288
Thr Leu Phe Ser Ile Asn Gln Ser Cys Leu Pro Gly Phe Tyr Thr Pro
                85                  90                  95

gct gaa ctg aag ccc ttc tgg gaa cgg cca cca cag gac ccc aat gcc   336
Ala Glu Leu Lys Pro Phe Trp Glu Arg Pro Pro Gln Asp Pro Asn Ala
            100                 105                 110

cct ggg gca gat gga aaa gca ttt cag aag agc aag tgg acc ccc ctg   384
Pro Gly Ala Asp Gly Lys Ala Phe Gln Lys Ser Lys Trp Thr Pro Leu
        115                 120                 125

gag acc cag gaa aag gaa gaa ggc tat aag aag cac tgt ttc aat gcc   432
Glu Thr Gln Glu Lys Glu Glu Gly Tyr Lys Lys His Cys Phe Asn Ala
    130                 135                 140

ttt gcc agc gac cgg atc tcc ctg cag agg tcc ctg ggg cca gac acc   480
Phe Ala Ser Asp Arg Ile Ser Leu Gln Arg Ser Leu Gly Pro Asp Thr
145                 150                 155                 160

cga cca cct gag tgt gtg gac cag aag ttc cgg cgc tgc ccc cca ctg   528
Arg Pro Pro Glu Cys Val Asp Gln Lys Phe Arg Arg Cys Pro Pro Leu
                165                 170                 175
```

```
gcc acc acc agc gtg atc att gtg ttc cac aac gaa gcc tgg tcc aca   576
Ala Thr Thr Ser Val Ile Ile Val Phe His Asn Glu Ala Trp Ser Thr
            180                 185                 190

ctg ctg cga aca gtg tac agc gtc cta cac acc acc cct gcc atc ttg   624
Leu Leu Arg Thr Val Tyr Ser Val Leu His Thr Thr Pro Ala Ile Leu
        195                 200                 205

ctc aag gag atc ata ctg gtg gat gat gcc agc aca gag gag cac cta   672
Leu Lys Glu Ile Ile Leu Val Asp Asp Ala Ser Thr Glu Glu His Leu
    210                 215                 220

aag gag aag ctg gag cag tac gtg aag cag ctg cag gtg gtg agg gtg   720
Lys Glu Lys Leu Glu Gln Tyr Val Lys Gln Leu Gln Val Val Arg Val
225                 230                 235                 240

gtg cgg cag gag gag cgg aag ggg ttg atc acc gcc cgg ctg ctg ggg   768
Val Arg Gln Glu Glu Arg Lys Gly Leu Ile Thr Ala Arg Leu Leu Gly
                245                 250                 255

gcc agc gtg gca cag gcg gag gtg ctc acg ttc ctg gat gcc cac tgt   816
Ala Ser Val Ala Gln Ala Glu Val Leu Thr Phe Leu Asp Ala His Cys
            260                 265                 270

gag tgc ttc cac ggc tgg ctg gag ccc ctc ctg gct cga atc gct gag   864
Glu Cys Phe His Gly Trp Leu Glu Pro Leu Leu Ala Arg Ile Ala Glu
        275                 280                 285

gac aag aca gtg gtg gtg agc cca gac atc gtc acc atc gac ctt aat   912
Asp Lys Thr Val Val Val Ser Pro Asp Ile Val Thr Ile Asp Leu Asn
    290                 295                 300

act ttt gag ttc gcc aag ccc gtc cag agg ggc aga gtc cat agc cga   960
Thr Phe Glu Phe Ala Lys Pro Val Gln Arg Gly Arg Val His Ser Arg
305                 310                 315                 320

ggc aac ttt gac tgg agc ctg acc ttc ggc tgg gaa aca ctt cct cca  1008
Gly Asn Phe Asp Trp Ser Leu Thr Phe Gly Trp Glu Thr Leu Pro Pro
                325                 330                 335

cat gag aag cag agg cgc aag gat gaa aca tac ccc atc aaa tcc ccg  1056
His Glu Lys Gln Arg Arg Lys Asp Glu Thr Tyr Pro Ile Lys Ser Pro
            340                 345                 350

acg ttt gct ggt ggc ctc ttc tcc atc ccc aag tcc tac ttt gag cac  1104
Thr Phe Ala Gly Gly Leu Phe Ser Ile Pro Lys Ser Tyr Phe Glu His
        355                 360                 365

atc ggt acc tat gat aat cag atg gag atc tgg gga ggg gag aac gtg  1152
Ile Gly Thr Tyr Asp Asn Gln Met Glu Ile Trp Gly Gly Glu Asn Val
    370                 375                 380

gaa atg tcc ttc cgg gtg tgg cag tgt ggg ggc cag ctg gag atc atc  1200
Glu Met Ser Phe Arg Val Trp Gln Cys Gly Gly Gln Leu Glu Ile Ile
385                 390                 395                 400

ccc tgc tct gtc gta ggc cat gtg ttc cgg acc aag agc ccc cac acc  1248
Pro Cys Ser Val Val Gly His Val Phe Arg Thr Lys Ser Pro His Thr
                405                 410                 415

ttc ccc aag ggc act agt gtc att gct cgc aat caa gtg cgc ctg gca  1296
```

```
Phe Pro Lys Gly Thr Ser Val Ile Ala Arg Asn Gln Val Arg Leu Ala
            420                 425                 430

gag gtc tgg atg gac agc tac aag aag att ttc tat agg aga aat ctg   1344
Glu Val Trp Met Asp Ser Tyr Lys Lys Ile Phe Tyr Arg Arg Asn Leu
        435                 440                 445

cag gca gca aag atg gcc caa gag aaa tcc ttc ggt gac att tcg gaa   1392
Gln Ala Ala Lys Met Ala Gln Glu Lys Ser Phe Gly Asp Ile Ser Glu
    450                 455                 460

cga ctg cag ctg agg gaa caa ctg cac tgt cac aac ttt tcc tgg tac   1440
Arg Leu Gln Leu Arg Glu Gln Leu His Cys His Asn Phe Ser Trp Tyr
465                 470                 475                 480

ctg cac aat gtc tac cca gag atg ttt gtt cct gac ctg acg ccc acc   1488
Leu His Asn Val Tyr Pro Glu Met Phe Val Pro Asp Leu Thr Pro Thr
                485                 490                 495

ttc tat ggt gcc atc aag aac ctc ggc acc aac caa tgc ctg gat gtg   1536
Phe Tyr Gly Ala Ile Lys Asn Leu Gly Thr Asn Gln Cys Leu Asp Val
            500                 505                 510

ggt gag aac aac cgc ggg ggg aag ccc ctc atc atg tac tcc tgc cac   1584
Gly Glu Asn Asn Arg Gly Gly Lys Pro Leu Ile Met Tyr Ser Cys His
        515                 520                 525

ggc ctt ggc ggc aac cag tac ttt gag tac aca act cag agg gac ctt   1632
Gly Leu Gly Gly Asn Gln Tyr Phe Glu Tyr Thr Thr Gln Arg Asp Leu
    530                 535                 540

cgc cac aac atc gca aag cag ctg tgt cta cat gtc agc aag ggt gct   1680
Arg His Asn Ile Ala Lys Gln Leu Cys Leu His Val Ser Lys Gly Ala
545                 550                 555                 560

ctg ggc ctt ggg agc tgt cac ttc act ggc aag aat agc cag gtc ccc   1728
Leu Gly Leu Gly Ser Cys His Phe Thr Gly Lys Asn Ser Gln Val Pro
                565                 570                 575

aag gac gag gaa tgg gaa ttg gcc cag gat cag ctc atc agg aac tca   1776
Lys Asp Glu Glu Trp Glu Leu Ala Gln Asp Gln Leu Ile Arg Asn Ser
            580                 585                 590

gga tct ggt acc tgc ctg aca tcc cag gac aaa aag cca gcc atg gcc   1824
Gly Ser Gly Thr Cys Leu Thr Ser Gln Asp Lys Lys Pro Ala Met Ala
        595                 600                 605

ccc tgc aat ccc agt gac ccc cat cag ttg tgg ctc ttt gtc tag       1869
Pro Cys Asn Pro Ser Asp Pro His Gln Leu Trp Leu Phe Val  *
    610                 615                 620
```

<210> 48
<211> 622
<212> PRT
<213> Homo sapiens

<400> 48

```
Met Arg Leu Leu Arg Arg Arg His Met Pro Leu Arg Leu Ala Met Val
 1               5                  10                  15
```

```
Gly Cys Ala Phe Val Leu Phe Leu Phe Leu Leu His Arg Asp Val Ser
            20                  25                  30
Ser Arg Glu Glu Ala Thr Glu Lys Pro Trp Leu Lys Ser Leu Val Ser
        35                  40                  45
Arg Lys Asp His Val Leu Asp Leu Met Leu Glu Ala Met Asn Asn Leu
    50                  55                  60
Arg Asp Ser Met Pro Lys Leu Gln Ile Arg Ala Pro Glu Ala Gln Gln
65                  70                  75                  80
Thr Leu Phe Ser Ile Asn Gln Ser Cys Leu Pro Gly Phe Tyr Thr Pro
                85                  90                  95
Ala Glu Leu Lys Pro Phe Trp Glu Arg Pro Pro Gln Asp Pro Asn Ala
            100                 105                 110
Pro Gly Ala Asp Gly Lys Ala Phe Gln Lys Ser Lys Trp Thr Pro Leu
        115                 120                 125
Glu Thr Gln Glu Lys Glu Glu Gly Tyr Lys Lys His Cys Phe Asn Ala
    130                 135                 140
Phe Ala Ser Asp Arg Ile Ser Leu Gln Arg Ser Leu Gly Pro Asp Thr
145                 150                 155                 160
Arg Pro Pro Glu Cys Val Asp Gln Lys Phe Arg Arg Cys Pro Pro Leu
                165                 170                 175
Ala Thr Thr Ser Val Ile Ile Val Phe His Asn Glu Ala Trp Ser Thr
            180                 185                 190
Leu Leu Arg Thr Val Tyr Ser Val Leu His Thr Thr Pro Ala Ile Leu
        195                 200                 205
Leu Lys Glu Ile Ile Leu Val Asp Asp Ala Ser Thr Glu Glu His Leu
    210                 215                 220
Lys Glu Lys Leu Glu Gln Tyr Val Lys Gln Leu Gln Val Val Arg Val
225                 230                 235                 240
Val Arg Gln Glu Glu Arg Lys Gly Leu Ile Thr Ala Arg Leu Leu Gly
                245                 250                 255
Ala Ser Val Ala Gln Ala Glu Val Leu Thr Phe Leu Asp Ala His Cys
            260                 265                 270
Glu Cys Phe His Gly Trp Leu Glu Pro Leu Leu Ala Arg Ile Ala Glu
        275                 280                 285
Asp Lys Thr Val Val Val Ser Pro Asp Ile Val Thr Ile Asp Leu Asn
    290                 295                 300
Thr Phe Glu Phe Ala Lys Pro Val Gln Arg Gly Arg Val His Ser Arg
305                 310                 315                 320
Gly Asn Phe Asp Trp Ser Leu Thr Phe Gly Trp Glu Thr Leu Pro Pro
                325                 330                 335
His Glu Lys Gln Arg Arg Lys Asp Glu Thr Tyr Pro Ile Lys Ser Pro
            340                 345                 350
Thr Phe Ala Gly Gly Leu Phe Ser Ile Pro Lys Ser Tyr Phe Glu His
        355                 360                 365
Ile Gly Thr Tyr Asp Asn Gln Met Glu Ile Trp Gly Gly Glu Asn Val
    370                 375                 380
Glu Met Ser Phe Arg Val Trp Gln Cys Gly Gly Gln Leu Glu Ile Ile
385                 390                 395                 400
Pro Cys Ser Val Val Gly His Val Phe Arg Thr Lys Ser Pro His Thr
                405                 410                 415
Phe Pro Lys Gly Thr Ser Val Ile Ala Arg Asn Gln Val Arg Leu Ala
            420                 425                 430
Glu Val Trp Met Asp Ser Tyr Lys Lys Ile Phe Tyr Arg Arg Asn Leu
        435                 440                 445
Gln Ala Ala Lys Met Ala Gln Glu Lys Ser Phe Gly Asp Ile Ser Glu
    450                 455                 460
Arg Leu Gln Leu Arg Glu Gln Leu His Cys His Asn Phe Ser Trp Tyr
465                 470                 475                 480
Leu His Asn Val Tyr Pro Glu Met Phe Val Pro Asp Leu Thr Pro Thr
                485                 490                 495
Phe Tyr Gly Ala Ile Lys Asn Leu Gly Thr Asn Gln Cys Leu Asp Val
```

```
            500                 505                 510
Gly Glu Asn Asn Arg Gly Gly Lys Pro Leu Ile Met Tyr Ser Cys His
        515                 520                 525
Gly Leu Gly Gly Asn Gln Tyr Phe Glu Tyr Thr Thr Gln Arg Asp Leu
    530                 535                 540
Arg His Asn Ile Ala Lys Gln Leu Cys Leu His Val Ser Lys Gly Ala
545                 550                 555                 560
Leu Gly Leu Gly Ser Cys His Phe Thr Gly Lys Asn Ser Gln Val Pro
                565                 570                 575
Lys Asp Glu Glu Trp Glu Leu Ala Gln Asp Gln Leu Ile Arg Asn Ser
            580                 585                 590
Gly Ser Gly Thr Cys Leu Thr Ser Gln Asp Lys Lys Pro Ala Met Ala
        595                 600                 605
Pro Cys Asn Pro Ser Asp Pro His Gln Leu Trp Leu Phe Val
    610                 615                 620
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<210> 49
<211> 1544
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (87)...(1517)

<400> 49

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gtggccggga gaaagtgtct ctcatttagg agggtttgca ggtccagagt aaagtcactg 60
aagagtggaa gcgaggaagg aacagg atg att aga cct cag ctg cgg acc gcg  113
                            Met Ile Arg Pro Gln Leu Arg Thr Ala
                             1               5

ggg ctg gga cga tgc ctc ctg ccg ggg ctg ctg ctg ctc ctg gtg ccc  161
Gly Leu Gly Arg Cys Leu Leu Pro Gly Leu Leu Leu Leu Leu Val Pro
 10                  15                  20                  25

gtc ctc tgg gcc ggg gct gaa aag cta cat acc cag ccc tcc tgc ccc  209
Val Leu Trp Ala Gly Ala Glu Lys Leu His Thr Gln Pro Ser Cys Pro
                 30                  35                  40

gcg gtc tgc cag ccc acg cgc tgc ccc gcg ctg ccc acc tgc gcg ctg  257
Ala Val Cys Gln Pro Thr Arg Cys Pro Ala Leu Pro Thr Cys Ala Leu
             45                  50                  55

ggg acc acg ccg gtg ttc gac ctg tgc cgc tgt tgc cgc gtc tgc ccc  305
Gly Thr Thr Pro Val Phe Asp Leu Cys Arg Cys Cys Arg Val Cys Pro
         60                  65                  70

gcg gcc gag cgt gaa gtc tgc ggc ggg gcg cag ggc caa ccg tgc gcc  353
Ala Ala Glu Arg Glu Val Cys Gly Gly Ala Gln Gly Gln Pro Cys Ala
     75                  80                  85

ccg ggg ctg cag tgc ctc cag ccg ctg cgc ccc ggg ttc ccc agc acc  401
Pro Gly Leu Gln Cys Leu Gln Pro Leu Arg Pro Gly Phe Pro Ser Thr
 90                  95                 100                 105

tgc ggt tgc ccg acg ctg gga ggg gcc gtg tgc ggc agc gac agg cgc  449
Cys Gly Cys Pro Thr Leu Gly Gly Ala Val Cys Gly Ser Asp Arg Arg
                110                 115                 120

acc tac ccc agc atg tgc gcg ctc cgg gcc gaa aac cgc gcc gcg cgc  497
```

```
Thr Tyr Pro Ser Met Cys Ala Leu Arg Ala Glu Asn Arg Ala Ala Arg
            125                 130                 135

cgc ctg ggc aag gtc ccg gcc gtg cct gtg cag tgg ggg aac tgc ggg   545
Arg Leu Gly Lys Val Pro Ala Val Pro Val Gln Trp Gly Asn Cys Gly
        140                 145                 150

gat aca ggg acc aga agc gca ggc ccg ctc agg agg aat tac aac ttc   593
Asp Thr Gly Thr Arg Ser Ala Gly Pro Leu Arg Arg Asn Tyr Asn Phe
    155                 160                 165

atc gcc gcg gtg gtg gag aag gtg gcg cca tcg gtg gtt cac gtg cag   641
Ile Ala Ala Val Val Glu Lys Val Ala Pro Ser Val Val His Val Gln
170                 175                 180                 185

ctg tgg ggc agg tta ctt cac ggc agc agg ctt gtt cct gtg tac agt   689
Leu Trp Gly Arg Leu Leu His Gly Ser Arg Leu Val Pro Val Tyr Ser
                190                 195                 200

ggc tct ggg ttc ata gtg tct gag gac ggg ctc att att acc aat gcc   737
Gly Ser Gly Phe Ile Val Ser Glu Asp Gly Leu Ile Ile Thr Asn Ala
            205                 210                 215

cat gtt gtc agg aac cag cag tgg att gag gtg gtg ctc cag aat ggg   785
His Val Val Arg Asn Gln Gln Trp Ile Glu Val Val Leu Gln Asn Gly
        220                 225                 230

gcc cgt tat gaa gct gtt gtc aag gat att gac ctt aaa ttg gat ctt   833
Ala Arg Tyr Glu Ala Val Val Lys Asp Ile Asp Leu Lys Leu Asp Leu
    235                 240                 245

gcg gtg att aag att gaa tca aat gct gaa ctt cct gta ctg atg ctg   881
Ala Val Ile Lys Ile Glu Ser Asn Ala Glu Leu Pro Val Leu Met Leu
250                 255                 260                 265

gga aga tca tct gac ctt cgg gct gga gag ttt gtg gtg gct ttg ggc   929
Gly Arg Ser Ser Asp Leu Arg Ala Gly Glu Phe Val Val Ala Leu Gly
                270                 275                 280

agc cca ttt tct ctg cag aac aca gct act gca gga att gtc agc acc   977
Ser Pro Phe Ser Leu Gln Asn Thr Ala Thr Ala Gly Ile Val Ser Thr
            285                 290                 295

aaa cag cga ggg ggc aaa gaa ctg ggg atg aag gat tca gat atg gac  1025
Lys Gln Arg Gly Gly Lys Glu Leu Gly Met Lys Asp Ser Asp Met Asp
        300                 305                 310

tac gtc cag att gat gcc aca att aac tat ggg aat tct ggt ggt cct  1073
Tyr Val Gln Ile Asp Ala Thr Ile Asn Tyr Gly Asn Ser Gly Gly Pro
    315                 320                 325

ctg gtg aac ttg gat ggt gat gtg att ggc gtc aat tca ttg agg gtg  1121
Leu Val Asn Leu Asp Gly Asp Val Ile Gly Val Asn Ser Leu Arg Val
330                 335                 340                 345

act gat gga atc tcc ttt gca att cct tca gat cga gtt agg cag ttc  1169
Thr Asp Gly Ile Ser Phe Ala Ile Pro Ser Asp Arg Val Arg Gln Phe
                350                 355                 360

ttg gca gaa tac cat gag cac cag atg aaa gga aag gcg ttt tca aat  1217
Leu Ala Glu Tyr His Glu His Gln Met Lys Gly Lys Ala Phe Ser Asn
```

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            365                 370                 375

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Glu Glu Leu Lys Met His Tyr Pro Asp Phe Pro Asp Val Ser Ser Gly
    395                 400                 405

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Val Tyr Val Cys Lys Val Val Glu Gly Thr Ala Ala Gln Ser Ser Gly
410                 415                 420                 425

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Thr Thr Thr Asp Val Val Lys Ala Leu Asp Ser Asp Ser Leu Ser Met
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Cys Pro Ala Leu Pro Thr Cys Ala Leu Gly Thr Thr Pro Val Phe Asp
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Gly Gly Ala Gln Gly Gln Pro Cys Ala Pro Gly Leu Gln Cys Leu Gln
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Pro Leu Arg Pro Gly Phe Pro Ser Thr Cys Gly Cys Pro Thr Leu Gly
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Gly Ala Val Cys Gly Ser Asp Arg Arg Thr Tyr Pro Ser Met Cys Ala
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Leu Arg Ala Glu Asn Arg Ala Ala Arg Arg Leu Gly Lys Val Pro Ala
    130                 135                 140
Val Pro Val Gln Trp Gly Asn Cys Gly Asp Thr Gly Thr Arg Ser Ala
145                 150                 155                 160
Gly Pro Leu Arg Arg Asn Tyr Asn Phe Ile Ala Ala Val Val Glu Lys
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Val Ala Pro Ser Val Val His Val Gln Leu Trp Gly Arg Leu Leu His
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        355                 360                 365
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         35                  40                  45
```

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Lys His Gly Lys Glu Glu Arg Tyr Glu Pro Glu Val Gln Tyr Gln Met
 65                  70                  75                  80

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                165                 170                 175

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Gln Glu Glu Gln Asp Pro Ala Asn His Thr Cys Gly Val Lys Ser Thr
            180                 185                 190

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Asp Gly Lys Gln Gly Pro Ile Arg Ile Ser Arg Ser Leu Lys Ser Pro
        195                 200                 205

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        275                 280                 285

aac ttc ctg aga tgg cac agt tct aac ctg ggg aaa aag atc cac gac   972
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            420                 425                 430

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        435                 440                 445

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: **MILLENNIUM PHARMACEUTICALS, INC.** [US/US]; 40 Landsdowne Street, Cambridge, MA 02139 (US).

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(74) Agent: **SIOUSSAT, Tracy, M.**; Millennium Pharmaceuticals, INC., 40 Landsdowne Street, Cambridge, MA 02139 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS AND COMPOSITIONS FOR TREATING AIDS AND HIV-RELATED DISORDERS USING 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, OR 46777

(57) Abstract: The present invention relates to methods for the diagnosis and treatment of AIDS or an HIV-related disorder or disorders. Specifically, the present invention identifies the differential expression of 9145, 1725, 311, 837, 58305, 156, 14175, 50352, 32678, 5560, 7240, 8865, 12396, 12397, 13644, 19938, 2077, 1735, 1786, 10220, 17822, 33945, 43748, 47161, 81982, and 46777 genes in tissues relating to AIDS or an HIV-related disorder, relative to their expression in normal, or non-AIDS or HIV-related disease states, and/or in response to manipulations relevant to AIDS or an HIV-related disorder. The present invention describes methods for the diagnostic evaluation and prognosis of various HIV-related disorders, and for the identification of subjects exhibiting a predisposition to such conditions. The invention also provides methods for identifying a compound capable of modulating AIDS or an HIV-related disorder or disorders. The present invention also provides methods for the identification and therapeutic use of compounds as treatments of AIDS or an HIV-related disorder.

WO 2004/080535 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/06120

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/70; G01N 33/53
US CL : 435/5, 7.1, 7.71
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/5, 7.1, 7.71

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPATFUL, WPIDS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/0052032 A1 (MEYERS, R., et al.) 02 May 2002 (02.05.2002), see entire document.	1-20
A	US 2002/0042371 A1 (MEYERS, R., et al.) 11 April 2002 (11.04.2002), see entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
13 September 2004 (13.09.2004)

Date of mailing of the international search report
05 OCT 2004

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Commissioner for Patents
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Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
JS Parkin
Telephone No. (703) 308-1111

Form PCT/ISA/210 (second sheet) (January 2004)

Abstract

SUSTIVA (efavirenz) 600 mg film-coated tablets

Background:

Sustiva (Efavirenz) Oral Solution is approved for children ≥ 3 years of age in Europe only. Efavirenz capsule contents mixed with food vehicles will be one of the modes of administration in pediatric study, AI266922, which will be conducted to gain approval of oral solution in children < 3 years of age worldwide.

Methods:

Open-label, three-period, three-treatment cross over study with two treatment groups in twenty-four healthy subjects (12 subjects / treatment group). Treatment Group 1 received treatments A (3 x 200 mg EFV intact capsule fasted), B (EFV capsule contents + applesauce) and C (EFV capsule contents + grape jelly). Treatment Group 2 will receive treatments A, D (EFV capsule contents + yogurt), and E (EFV capsule contents + baby formula).

Abstract

SUSTIVA (efavirenz) 600 mg film-coated tablets

Results:

All comparisons of Treatments B and C to Reference Treatment A met the criteria for bioequivalence with respect to AUC(INF) and AUC(0-T). Although Cmax did not meet the criteria for bioequivalence, mean Cmax for Treatments B and C were within 7% of the mean Cmax for Reference Treatment A. Treatment E was bioequivalent to Reference Treatment A with respect to Cmax, AUC(INF), and AUC(0-T). With respect to AUC(INF) and AUC(0-T), the bioavailability of treatment D was bioequivalent to Reference Treatment A. Mean Cmax for Treatment D was approximately 17% higher compared to Reference Treatment A and did not meet bioequivalence criteria.

Conclusions:

The AUC of efavirenz from capsule contents mixed and administered with each of the food vehicles (applesauce, grape jelly, yogurt) or baby formula, was bioequivalent to the AUC of the intact capsule formulation administered under fasted conditions. Efavirenz can be administered with applesauce, grape jelly, yogurt, or baby formula. Grape jelly was the most palatable food vehicle used to administer efavirenz capsule contents.

Background

SUSTIVA (efavirenz) 600 mg film-coated tablets

- Non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1 infection in combination with other medications
- Capsule approved for children ≥ 3 years of age
- Oral Solution approved for children ≥ 3 years of age in Europe only
- Pediatric study AI266922: To gain approval of oral solution in children < 3 years of age worldwide
  - EFV capsule contents mixed with food vehicles will be one of the modes of administration
- Recommended by the FDA as a prerequisite to the EFV pediatric trial
  - **Relative bioavailability of the new formulation compared to the adult formulation** (US FDA DRAFT Guidance on General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products; Nov 10, 1998)

Objectives

SUSTIVA (efavirenz) 600 mg film-coated tablets

- **Primary Objective:** To assess the bioavailability of efavirenz capsule contents when mixed with one of three food vehicles (applesauce, grape jelly, or yogurt) or baby formula, relative to the intact capsule formulation administered under fasted conditions.
- **Secondary Objective:** To assess the safety of efavirenz.

Methods: Study Design

S-R-

Treatment Group I (ABC)	A	-W-	B	-W-	C	— D
	A	-W-	C	-W-	B	
	B	-W-	A	-W-	C	
	B	-W-	C	-W-	A	
	C	-W-	A	-W-	B	
	C	-W-	B	-W-	A	
Treatment Group II (ADE)	A	-W-	D	-W-	E	
	A	-W-	E	-W-	D	
	D	-W-	A	-W-	E	
	D	-W-	E	-W-	A	
	E	-W-	A	-W-	D	
	E	-W-	D	-W-	A	
	Period 1 (Day 1)		Period 2 (Day 21)		Period 3 (Day 41)	

S = Screening, R = Randomization, W = ≥ 20-day Washout, D = Study Discharge (Day 61)

Treatment A: 600 mg (3x200 mg) EFV intact capsule (fasted)

Treatment B: 600 mg (3x200 mg) EFV capsule contents mixed with 2 teaspoons of Mott's® Natural Applesauce

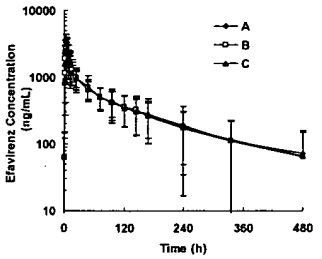
Treatment C: 600 mg (3x200 mg) EFV capsule contents mixed with 2 teaspoons of Smucker's® Grape Jelly.

Treatment D: 600 mg (3x200 mg) EFV capsule contents mixed with 2 teaspoons of Stonyfield Farm® Organic Whole Milk Plain Yogurt

Treatment E: 600 mg (3x200 mg) EFV capsule contents mixed with 10 ml of Enfamil® Baby Formula.

Results

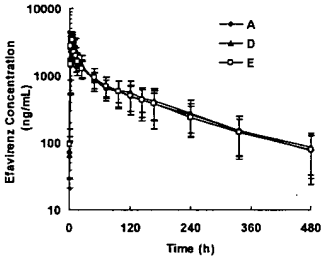
Figure 1A: Semilog Plot of Mean (SD) Plasma Concentration – Time Profile (0 - 480 hours) of Efavirenz for Treatment Group ABC



A = 3x200 mg capsules fasted
B = 3x200 mg + applesauce
C = 3x200 mg + grape jelly

Results

Figure 1B: Semilog Plot of Mean (SD) Plasma Concentration – Time Profile (0 - 480 hours) of Efavirenz for Treatment Group ADE



A = 3x200 mg capsules fasted
D = 3x200 mg + yogurt
E = 3x200 mg + baby formula

Results

Table 1A: Summary Statistics for Efavirenz Pharmacokinetic Parameters by Group and Treatment

Group	Treatment *	Efavirenz Pharmacokinetic Parameters				
		Cmax (ng/mL) Geom. Mean (CV %)	AUC(INF) (ng.h/mL) Geom. Mean (CV %)	AUC(0-T) (ng.h/mL) Geom. Mean (CV %)	Tmax (h) Median (min, max)	T-HALF (h) Mean (SD)
ABC (n = 10)	A	2693 (48%)	153067 (55%)	142788 (45%)	4.5 (2.0, 8.0)	117 (53)
	B	2475 (63%)	143269 (61%)	133213 (48%)	4.0 (2.0, 8.0)	125 (69)
	C	2772 (37%)	150170 (71%)	136038 (46%)	3.0 (1.0, 5.0)	149 (139)
ADE (n = 12)	A	3522 (29%)	192825 (39%)	179718 (36%)	3.0 (2.0, 4.0)	122 (40)
	D	4114 (27%)	219003 (32%)	204139 (29%)	4.0 (1.0, 12.0)	127 (41)
	E	3794 (23%)	202967 (33%)	189881 (30%)	4.0 (1.0, 12.0)	127 (39)

* A = 3x200 mg capsules fasted, B = 3x200 mg + applesauce, C = 3x200 mg + grape jelly, D = 3x200 mg + yogurt, E = 3x200 mg + baby formula

Results

Table 1B: Statistical Analysis Results for Efavirenz Cmax, AUC(0-T), and AUC(INF) for Treatment Group ABC

Pharmacokinetic Variable	Geometric Means		Ratio of Geometric Means		
	Treatment *	Geometric Mean	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	2625			
	B	2461	B vs A	0.938	(0.755, 1.164)
	C	2710	C vs A	1.032	(0.832, 1.282)
AUC(0-T) (ng*h/mL)	A	138770			
	B	130289	B vs A	0.939	(0.836, 1.054)
	C	132680	C vs A	0.956	(0.852, 1.074)
AUC(INF) (ng*h/mL)	A	147408			
	B	138930	B vs A	0.943	(0.807, 1.101)
	C	144630	C vs A	0.981	(0.840, 1.146)

* A = 3x200 mg capsules fasted, B = 3x200 mg + applesauce, C = 3x200 mg + grape jelly, D = 3x200 mg + yogurt, E = 3x200 mg + baby formula

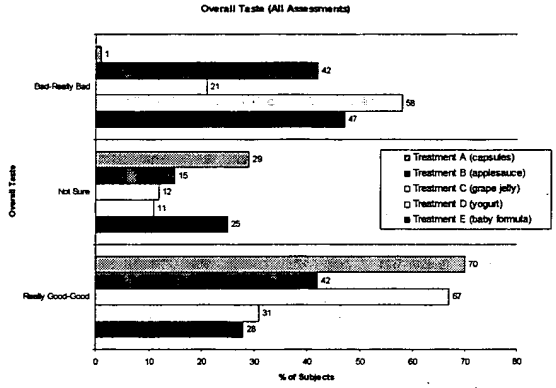
Results

Table 1C: Statistical Analysis Results for Efavirenz Cmax, AUC(0-T), and AUC(INF) for Treatment Group ADE

Pharmacokinetic Variable	Geometric Means		Ratio of Geometric Means		
	Treatment *	Geometric Mean	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	3521			
	D	4114	D vs A	1.168	(1.042, 1.310)
	E	3794	E vs A	1.077	(0.961, 1.208)
AUC(0-T) (ng*h/mL)	A	179718			
	D	204139	D vs A	1.136	(1.070, 1.206)
	E	189881	E vs A	1.057	(0.995, 1.122)
AUC(INF) (ng*h/mL)	A	192826			
	D	219003	D vs A	1.136	(1.075, 1.200)
	E	202967	E vs A	1.053	(0.996, 1.112)

* A = 3x200 mg capsules fasted, B = 3x200 mg + applesauce, C = 3x200 mg + grape jelly, D = 3x200 mg + yogurt, E = 3x200 mg + baby formula

Results



Conclusions

- The AUC of efavirenz from capsule contents mixed and administered with each of the food vehicles (applesauce, grape jelly, yogurt) or baby formula, was bioequivalent to the AUC of the intact capsule formulation administered under fasted conditions.
- Efavirenz can be administered with applesauce, grape jelly, yogurt, or baby formula.
- Grape jelly was the most palatable food vehicle used to administer efavirenz capsule contents.

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